5.08 INSULIN GLARGINE, injection, 300 units per mL, Toujeo®, Sanofi Aventis Australia Pty Ltd.

1 Purpose of Application

1.1 An unrestricted listing for insulin glargine 300 units/mL (U300). The ACPM recommended indication is for the treatment of adults with diabetes mellitus.

2 Requested listing

2.1 The submission sought the following unrestricted listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Effective Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
INSULIN GLARGINE injection, 300 international units/mL, 1 x 1.5 mL cartridge	1	1	$[redacted]	Toujeo	Sanofi
INSULIN GLARGINE injection, 300 international units/mL, 3 x 1.5 mL cartridge	5	1	$[redacted]	Toujeo	Sanofi
INSULIN GLARGINE injection, 300 international units/mL, 5 x 1.5 mL cartridge	5	1	$[redacted]	Toujeo	Sanofi

2.2 The requested prices in the submission were stated to be effective prices. The sponsor intended to request a Special Pricing Arrangement for the U300 formulation based on the price for the insulin glargine 100 units/mL (U100; Lantus) formulation.

2.3 For type 1 diabetes mellitus (T1DM) listing was requested on a cost-minimisation basis compared with U100. For type 2 diabetes mellitus (T2DM) listing was requested on a cost-effectiveness basis compared with U100.

2.4 An unrestricted listing was proposed for U300 and thus the PBS population was potentially broader than the ACPM suggested indication, in adults, and the trial populations. In particular, the PBS population may include patients with an HbA1c <7% and >10%, T1DM patients aged <18 years, insulin naïve T1DM patients and insulin experienced T2DM patients treated with lower doses of basal insulin.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. TOUJEO insulin glargine 300 units/mL solution for injection injector pen was registered on 30 June 2015.

3.2 U300 has not been considered by the PBAC previously.

3.3 U100 was recommended for listing as an unrestricted benefit on a cost-effectiveness basis versus insulin NPH at an extraordinary PBAC meeting on 29 March 2006. The recommendation was on the basis of a reduction in hypoglycaemic events with U100 compared with insulin NPH. With U100 the risk of symptomatic hypoglycaemia in T1DM was estimated to be reduced by 10%, from 43.32 to 39.00 events/patient/year (March 2006 PBAC Public Summary Document (PSD)). The current submission claimed a reduction in hypoglycaemia in T2DM, and the risk of symptomatic hypoglycaemia with U100 in the T2DM trials presented is substantially lower (3.76 to 14.76 events/patient/year).

3.4 U300 is supplied in 1.5mL cartridges sealed into a disposable pen injector. A single cartridge (1.5 mL) of U300 contains 450 units of insulin glargine. A single cartridge (3.0 mL) of U100 contains 300 units of insulin glargine. If the shelf-life for both products is the same (28 days), the increase in the number of units per cartridge may result in increased wastage, especially in T2DM. The ACPM was concerned that if a 42-day open shelf life was accepted, then this could cause confusion among diabetes educators and patients because a standard open shelf life of 28 days applied to all the other insulin products. The ACPM noted that a 42 day open shelf life for this product had not been accepted by the EMA or FDA and advised that the open shelf life should be 28 days.

3.5 Three pack sizes (1, 3 and 5 pens) are proposed for the U300 listing. One pack size (5 cartridges/pens) is listed for U100.

3.6 The single cartridge pack was intended for patients currently using insulin pump therapy as a back-up supply of basal insulin should there be a malfunction of their insulin pump. In most cases the back-up basal insulin supply is not used, and, once it passes it usable shelf life, is discarded. The availability of a single cartridge pack was to reduce the additional wastage which would occur if only multiple cartridge packs were available. Similarly, the 3 pack was to allow patients who require lower doses to avoid the wastage that would otherwise occur if only a 5 pack was available.

4 Clinical place for the proposed therapy

4.1 Patients with T1DM cannot produce insulin and require lifelong insulin replacement therapy. Patients with T2DM produce insulin, but may not produce enough of it or cannot use it effectively.

4.2 The submission proposed U300 as an alternative basil insulin treatment. A formulation of insulin glargine (100 units/mL) is already PBS listed. U300 is a more concentrated form of insulin glargine (300 units/mL).

5 Comparator

5.1 Insulin glargine 100 units per mL (U100). The ESC considered this was the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

The PBAC noted and welcomed the input from individuals (2) and health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with U300 including: less nocturnal hypoglycaemia; smaller volumes of insulin required will be more convenient for patients with T2DM with severe insulin resistance requiring large doses of insulin and may mean better compliance; and insulin expected to last beyond 24 hours may reduce the need for a second daily dose.

Clinical trials

6.2 The submission was based on three head-to-head trials comparing U300 to U100 in T2DM (EDITION I, EDITION II and EDITION III) and one head-to-head trial in T1DM (EDITION IV).

6.3 Two head-to-head trials of U300 and U100 were excluded from the submission due to being conducted in Japan only (EDITION JPI and EDITION JPII). The submission stated EDITION JPI was similar in design to EDITION IV, and EDITION JPII was similar in design to EDITION II. No results were provided in the submission for the excluded trials. Based on conference abstracts located during the evaluation, the results of the excluded trials appear consistent with those for the included trials. The ESC considered the exclusion of these trials may not be appropriate given the EDITION trials included in the submission are multinational.

6.4 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
EDITION I	EFC11628: 6-Month, Multicentre, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both plus Mealtime Insulin in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period	23 December 2013
	Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1)	Diabetes Care 2014; 37:2755–62
	Riddle MC, Yki-Jarvinen H, Bolli GB, Ziemen M, Muehlen-Bartmer I, Cissokho S, et al. Sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml vs 100 U/ml: 1-year results in type 2 diabetes with basal and mealtime insulin (EDITION 1)	Diabetologia 2014; 57 (Suppl. 1): S402
	Home PD, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Riddle MC. Investigational new insulin glargine U300: Glucose control and hypoglycaemia in people with Type 2 diabetes using a basal plus mealtime insulin regimen (EDITION I)	Diabetic Medicine 2014; 31 (Suppl. 1): 61

	Bolli GB, Home PD, Ziemen M, Muehlen-Bartmer I, Bizet F, Riddle MC. Investigational new insulin glargine U300: Glycaemic control and hypoglycaemia in type 2 diabetes using a mealtime+basal insulin regimen (edition I)	Diabetes Technology and Therapeutics 2014; 16: A89
	Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. New insulin glargine formulation: Glucose control and hypoglycaemia in people with type 2 diabetes using basal and mealtime insulin (EDITION I)	Diabetologia 2013; 56 (Suppl1): S97
	Riddle MC, Yki-Jarvinen H, Bolli GB, Cissokho S, Home PD. Sustained glycemic control and less hypoglycemia with new insulin glargine 300 u/ml vs 100 u/ml: 1-year results in t2dm with basal + mealtime insulin (EDITION 1)	Diabetes Technology and Therapeutics 2015; 17: A15
EDITION II	EFC11629: 6-Month, Multicentre, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® both in combination with oral anti hyperglycaemic drug(s) in Patients with Type 2 Diabetes Mellitus with a 6-month Safety Extension Period	23 December 2013
	Yki-Jarvinen H, Bergenstal R, Ziemen M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2)	Diabetes Care 2014; 37 (12): 3235-43
	Yki-Jarvinen H, Bergenstal RM, Bolli GB, Ziemen M, Wardecki M, Muehlen-Bartmer I, et al. Less nocturnal hypoglycaemia and weight gain with new insulin glargine 300 U/ml vs 100 U/ml: 1-year results in people with type 2 diabetes using basal insulin and OADs (EDITION 2)	Diabetologia 2014; 57 (Suppl.1): S387
	Bergenstal RM, Riddle MC, Ziemen M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. Investigational new insulin U300: Glucose control and hypoglycaemia in type 2 diabetes people on basal insulin and OADs (EDITION II)	Diabetes Technology and Therapeutics 2014; 16: A28
	Yki-Järvinen H, Bergenstal RM, Boll GB, Wardęcki M, Maroccia M and Riddle MC. Less nocturnal hypoglycaemia and weight gain with new insulin glargine 300 U/mL vs 100 U/mL: 1-year results in T2DM using basal insulin+OADs (EDITION 2)	Conference abstract, citation not provided in submission
EDITION III	EFC12347: 6-month, Multicentre, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® in Insulin-Naïve Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Non-Insulin Anti hyperglycaemic Drugs with a 6-month Safety Extension Period	10 January 2014
	Bolli GB, Riddle MC, Bergenstal RM, Ziemen M, Sestakauskas K et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3)	Diabetes, Obesity and Metabolism 2015; 17:386-394
	Bolli GB, Riddle MC, Bergenstal RM, Ziemen M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ML: Glycemic control and hypoglycemia in insulin naive people with T2DM (edition 3)	Diabetes 2014; 63: A19
	Bolli GB, Riddle MC, Bergenstal RM, Ziemen M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ml: Glycaemic control and hypoglycaemia in insulin-naive people with type 2 diabetes mellitus (EDITION 3)	Diabetologia 2014; 57 (Suppl.1): S387
EDITION IV	EFC12456: A 6-Month, Multicentre, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected in the Morning or Evening in Patients with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period	4 March 2014

Source: Table B.4, p38 of the submission; Attachments 3, 4, 5 and 6 of the submission

6.5 The key features of the direct randomised trials are summarised in the following table.

Table 2: Key features of the included evidence

Trial	N	Design/ duration/ dosing	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
EDITION I	807	R, OL, NI, MC, 6 months, evening dose	Low	T2DM treated with basal insulin plus mealtime insulin	HbA1c, ≥1Nocturnal severe and/or confirmed hypoglycaemia	Outcomes used in modelled evaluation are symptomatic and severe hypoglycaemia
EDITION II	811	R, OL, NI, MC, 6 months, evening dose	Low	T2DM treated with basal insulin plus OADs		
EDITION III	878	R, OL, NI, MC, 6 months, evening dose	Low	T2DM, insulin naïve, treated with non-insulin antihyperglycaemic drugs		
EDITION IV	549	R, OL, NI, MC, 6 months, randomised to morning or evening dose	Low	T1DM treated with basal insulin plus mealtime insulin	HbA1c, ≥1 Nocturnal severe and/or confirmed hypoglycaemia	NA

Abbreviations: HbA1c=glycosylated haemoglobin; MC=multi-centre; OADs=oral anti-diabetic drugs; OL=open label; NA=not applicable; NI = non-inferiority, R=randomised; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus
Source: compiled during the evaluation

6.6 The four trials were open-label with no blinding of either investigators or participants. The risk of bias due to lack of blinding is considered low for the primary efficacy outcome of HbA1c. The risk of bias is higher for the hypoglycaemia outcomes as participants on U300 treatment may be more likely to test for hypoglycaemic events. The pre-PBAC response considered if patients treated with U300 reported a higher rate of hypoglycaemic events due to increased testing, the difference between the U300 and U100 treatment arms would have been underestimated and, consequently, the true benefit of U300 in the reduction of the risk of hypoglycaemia would be underestimated. Any such bias would therefore benefit the comparator rather than U300.

6.7 The trial patients were likely to have had a higher risk of hypoglycaemia compared with patients treated in clinical practice due to aiming for lower glucose targets, and in EDITION I and II, due to enrolling patients with a long duration of disease and insulin use, and whose diabetes remained uncontrolled despite being on a high dose of basal insulin. Although the PSCR argued that the high doses of basal insulin would not result in a higher risk of hypoglycaemia, this contradicted the submission statement in Section C, page 151, which stated that patients enrolled in the EDITION I and II trials would be expected to have a high risk of hypoglycaemia. This is because the trials enrolled patients with inadequate glycaemic control whilst being treated with basal insulin, and the inadequate control may have been as a result of being unable to optimise the insulin dose due to hypoglycaemia.

6.8 Nocturnal severe and/or confirmed hypoglycaemia between the start of week 9 and month 6 was defined as a main secondary endpoint in EDITION I, II and III. A severe event required assistance of another person to actively administer carbohydrate, glucagon or other resuscitative action. A confirmed event required a measured plasma glucose concentration of ≤3.9 mmol/L occurring as soon as possible after a patient-recorded hypoglycaemic episode, and could be symptomatic or

asymptomatic. Nocturnal events occurred between 00:00 and 05:59 hours. Unless severe, this relies on patients being able to detect a hypoglycaemic event and in the case of nocturnal episodes, overnight. The ESC considered this would possibly overestimate the effectiveness in practice given patients with a history of hypoglycaemic unawareness were excluded from the trials.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative effectiveness

6.9 The HbA1c results for the direct randomised trials are summarised below.

Table 3: Mean change in HbA1c from baseline to month 6 (%) across the direct randomised trials

Trial ID	U300			U100			LS mean difference (95% CI)
	N	Baseline, mean (SD)	LS mean change (SE)	N	Baseline, mean (SD)	LS mean change (SE)	
EDITION I	404	8.14 (0.78)	-0.83 (0.060)	400	8.14 (0.76)	-0.83 (0.061)	-0.00 (-0.112, 0.107)
EDITION II	403	8.28 (0.87)	-0.57 (0.094)	405	8.22 (0.77)	-0.56 (0.093)	-0.01 (-0.139, 0.119)
EDITION III	402	8.49 (1.04)	-1.42 (0.047)	394	8.58 (1.07)	-1.46 (0.048)	0.04 (-0.090, 0.174)
EDITION IV	273	8.13 (0.77)	-0.40 (0.051)	273	8.12 (0.79)	-0.44 (0.051)	0.04 (-0.098, 0.185)

Abbreviations: CI=confidence interval; LS=least squares; SD=standard deviation; SE=standard error
Source: Table B.19, p63 of the submission

6.10 For the four trials the upper 95% confidence limit for the difference between the treatment groups was below the 0.3%-0.4% non-inferiority margin previously used by the PBAC.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

6.11 In the four trials a slightly higher proportion of patients treated with U300 had a treatment emergent adverse event compared with patients treated with U100 (the difference was statistically significant in EDITION II only; see Table 4 below). Most of the events were non-specific (e.g. viral infections and gastrointestinal disorders) and were not considered to be related to treatment.

6.12 In EDITION IV (T1DM) the incidence of hypoglycaemia was similar with U300 and U100.

6.13 In EDITION I, II and III (T2DM) there was a non-statistically significant trend for a lower incidence of hypoglycaemia in patients treated with U300. The difference between the treatment groups was generally larger for nocturnal events. The reduction in nocturnal events may be associated with the evening dosing and slower release of insulin glargine from the U300 formulation compared with the U100 formulation. The ACPM noted that the claimed reduction in severe and/or confirmed nocturnal hypoglycaemia was only in a subgroup of the target population (T2DM, evening dose).

6.14 In the four trials the incidence of severe hypoglycaemia was low and similar for both treatment groups.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Benefits/harms

6.15 A summary of the comparative benefits and harms for U300 versus U100 is presented in the following table.

Table 4: Summary of comparative benefits and harms for U300 and U100

Benefits							
Change from baseline to month 6 in HbA1c (%)							
Trial	U300			U100			Mean difference: U300 vs. U100 (95% CI)
	n	**Mean** Δ baseline	SE	n	**Mean** Δ baseline	SE	
EDITION I	404	-0.83	0.060	400	-0.83	0.061	-0.00 (-0.112, 0.107)
EDITION II	403	-0.57	0.094	405	-0.56	0.093	-0.01 (-0.139, 0.119)
EDITION III	402	-1.42	0.047	394	-1.46	0.048	0.04 (-0.090, 0.174)
EDITION IV	273	-0.40	0.051	273	-0.44	0.051	0.04 (-0.098, 0.185)
Proportion of patients with at least 1 severe and/or confirmed nocturnal hypoglycaemic event between the start of week 9 and month 6							
Trial	U300	U100	RR (95% CI)	Event rate/100 pts per 6 months		RD (95% CI)	
				U300	U100		
EDITION I	146/404	184/400	0.79 (0.67, 0.93)	36.1	46.0	-0.099 (-0.165, -0.031)	
EDITION II	87/403	113/405	0.77 (0.61, 0.99)	21.6	27.9	-0.063 (-0.122, -0.004)	
EDITION III	67/432	75/430	0.89 (0.66, 1.20)	15.5	17.4	-0.019 (-0.069, 0.030)	
EDITION IV	162/273	153/273	1.06 (0.92, 1.23)	59.3	56.0	0.033 (-0.050, 0.115)	
Harms							
Trial	U300	U100	RR (95% CI)	Event rate/100 pts per 6 months		RD (95% CI)	
				U300	U100		
Any treatment emergent adverse event (TEAE)							
EDITION I	228/404	218/402	1.04 (0.92, 1.18)	56.4	54.2	0.02 (-0.05, 0.09)	
EDITION II	237/403	206/406	1.16 (1.02, 1.31)	58.8	50.7	0.08 (0.01, 0.15)	
EDITION III	247/435	245/438	1.02 (0.90, 1.14)	56.8	55.9	0.01 (-0.06, 0.07)	
EDITION IV	167/274	160/275	1.05 (0.91, 1.20)	60.9	58.2	0.03 (-0.05, 0.11)	
Documented symptomatic hypoglycaemia (≤3.9 mmol/L)							
EDITION I	283/404	313/402	0.90 (0.83, 0.98)	70.0	77.9	-0.08 (-0.14, -0.02)	
EDITION II	200/403	233/406	0.86 (0.76, 0.89)	49.6	57.4	-0.08 (-0.15, -0.01)	
EDITION III	133/435	157/438	0.85 (0.71, 1.03)	30.6	35.8	-0.05 (-0.11, 0.01)	
EDITION IV	233/274	230/275	1.02 (0.95, 1.09)	85.0	83.6	0.01 (-0.05, 0.08)	
Severe hypoglycaemia							
EDITION I	20/404	23/402	0.87 (0.48, 1.55)	5.0	5.7	-0.01 (-0.04, 0.02)	
EDITION II	4/403	6/406	0.67 (0.19, 2.37)	1.0	1.5	-0.00 (-0.02, 0.01)	
EDITION III	4/435	4/438	1.00 (0.31, 3.23)	0.9	0.9	0.00 (-0.02, 0.02)	
EDITION IV	18/274	26/275	0.71 (0.41, 1.24)	6.6	9.5	-0.03 (-0.08, 0.02)	

Abbreviations: CI=confidence interval; RD=risk difference; RR=risk ratio; SE=standard error. Source: Table B.19, p63; Table B.20, p65; Table B.33, p86; Table B.39, p119; Table B.42, p124; Table B.45, 128; Table B.48, p132 of the submission.

6.16 On the basis of one head-to-head trial (EDITION IV) presented in the submission, U300 appears to have the same effect as U100 in the treatment of T1DM. On the basis of three head-to-head trials (EDITION I, II and III), U300 appears to have the same effect as U100 in the treatment of T2DM. For T1DM and T2DM, the outcome assessed was glycosylated haemoglobin.

6.17 On the basis of one head-to-head trial (EDITION IV), the frequency of adverse events appears to be the same for U300 and U100 in the treatment of T1DM.

6.18 On the basis of three head-to-head trials (EDITION I, II and III), with the possible exception of hypoglycaemia, the frequency of adverse events appears to be the same for U300 and U100 in the treatment of T2DM. Based on two of the trials in patients previously treated with insulin (EDITION I and II), U300 given at night appears less likely to cause hypoglycaemia during the night compared to night-time dosing of U100. Per 100 patients treated, 6-10 are less likely to have severe and/or confirmed hypoglycaemia during the night over a maximum duration of follow-up of 6 months. However, there was no evidence of a difference in severe hypoglycaemia in EDITION I and II. Based on the third trial in patients not previously treated with insulin (EDITION III), the frequency of severe and/or confirmed hypoglycaemic events was similar for U300 and U100.

6.19 On the basis of three head-to-head trials (EDITION I, II and III), the frequency of severe hypoglycaemic events, defined as an event requiring assistance from another person to actively administer carbohydrate, glucagon or other resuscitative action, appears to be the same for U300 and U100.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical claim

6.20 For the treatment of T1DM the submission describes U300 as non-inferior in terms of comparative effectiveness and comparative safety over U100. The ESC considered this claim was adequately supported.

6.21 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.22 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

6.23 For the treatment of T2DM the submission describes U300 as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety (reduced risk of hypoglycaemia) over U100. The ESC considered the claim of non-inferiority for comparative effectiveness was adequately supported. The ESC considered the clinical significance of the claimed reduction in hypoglycaemia was questionable given:

- A statistically significant reduction in the proportion of patients with at least one nocturnal severe and/or confirmed hypoglycaemic event between the start of week 9 and month 6 was observed with U300 in EDITION I and II but not EDITION III.
- In the three trials patients were dosed in the evening, and a reduction in nocturnal hypoglycaemia with U300 may not be observed for patients dosed at other times

of the day. Evidence comparing the impact of the time of injection on the occurrence of hypoglycaemia in T2DM is not available (PSCR)

- The incidence of hypoglycaemia in the trials may be higher than in clinical practice due to the aggressive glucose targets, and in EDITION I and II, due to enrolling patients with a range of risk factors for hypoglycaemia (e.g. uncontrolled diabetes despite high doses of basal insulin, long duration of disease, long duration of insulin therapy). Additionally, patients with a history of hypoglycaemic unawareness were excluded from the trials.
- A reduction in the incidence of severe hypoglycaemia was not observed with U300 in any of the trials, noting that the EDITION trials were not powered to detect a difference in severe events alone.

6.24 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.25 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.26 Cost-minimisation analysis for T1DM: The submission estimated that U300 40.46 units daily and U100 34.12 units daily were equi-effective (i.e. 1 unit of U300 is equivalent to 0.84 units of U100). The equi-effective doses were based on the mean doses at 6 months in EDITION IV. The equi-effective doses differed for morning versus evening dosing. For patients dosed in the morning, 1 unit of U300 was equivalent to 0.90 units of U100. For patients dosed in the evening, 1 unit of U300 was equivalent to 0.78 units of U100. In EDITION IV approximately 50% of patients were dosed in the evening and 50% in the morning. The PSCR stated that data on the relative proportions of patients dosing at different times of the day in Australian clinical practice were not available.

6.27 In EDITION IV, at month 6 the mean daily mealtime insulin dose was higher for patients randomised to U300 compared with U100 (28.66 vs 27.11 units). The cost of mealtime insulin was not included in the T1DM economic analysis. Including the cost of mealtime insulin reduces the cost-minimisation ex-manufacturer price for U300 from $[redacted] to approximately $[redacted] per 450 unit pen.

6.28 Cost-effectiveness analysis for T2DM: In the submission each of the EDITION trials were modelled separately and sequentially (i.e. EDITION III followed by EDITION II followed by EDITION I). The models presented were an adaption of the model included in the March 2006 U100 PBAC submission in which a disutility was applied for symptomatic and severe hypoglycaemic events and for fear of future events. In the clinical trials symptomatic and severe hypoglycaemia were safety endpoints. The difference between the U300 and U100 treatment groups was not statistically significant (in post-hoc analyses) for symptomatic events in EDITION I and II and for severe events in the three trials. In the trials there was no difference between the treatment groups in the perceived frequency of hypoglycaemia, fear of hypoglycaemia or EQ-5D utility scores.

6.29 The Public Summary Document for the March 2006 U100 submission notes that the PBAC had a number of major concerns with the economic model for the listing of U100, and the PBAC's recommendation did not rely on the model presented. The following PBAC concerns were not addressed in this submission:

- The utility gain associated with a reduction in fear of future events may only arise in a small subset of patients with a directly perceptible reduction in hypoglycaemic events. The PSCR disagreed and suggested that all patients in the trials who experienced hypoglycaemic events were at risk of fear of hypoglycaemia, and the risk increased with repeated episodes, and likewise decreased as the number of events reduced. However, the ESC considered the argument that there was a significant difference in reduced fear of hypoglycaemia between treatment groups to be flawed given the data collected in the EDITION trials suggested there is no difference between the U300 and U100 treatment groups in perceived frequency of hypoglycaemia, fear of hypoglycaemia or EQ-5D utility scores. The PBAC agreed with the ESC that this was a significant issue with the model and did not believe the argument in the pre-PBAC response that the lack of a significant difference in fear of hypoglycaemia in the trials was due to the fact that majority of patients had experienced a hypoglycaemic event and therefore most patients were at risk of fear of hypoglycaemia.
- The health states used for the time trade off (TTO) study described a typical week and did not capture the chronic nature of the disease, in which there will be considerable variability in symptoms over time.
- The assumption inherent in the disutilities for fear of hypoglycaemia is that hypoglycaemic events disappear upon treatment with U300 (based on the way the disutilities from the TTO study have been calculated), whereas in reality these events occur at a reduced rate.
- The model is independent of the time horizon due to the event rates, costs and disutilities being the same for every 3 month cycle.

6.30 In the sequential model the hypoglycaemic event rates from EDITION III were applied for 3.75 years, the rates from EDITION II for 2.75 years and the rates from EDITION I for 13.5 years. The three trials enrolled distinct patient populations based on diabetes treatments received. The PBAC noted the Pre-PBAC response continued to argue the differences in the patient populations made them appropriate for use in the sequential model, but the Committee agreed with the ESC that the patient populations in the EDITION I, II and III trials do not reflect the continuum of disease progression. Thus, the sequential model does not appropriately address the concern regarding the use of constant event rates and is not a reliable construct for the economic evaluation.

Table 5: Summary of model structure and rationale

Component	Summary
Time horizon	20 years in the model base case versus 6 months in trials. The individual trial models are independent of the time horizon.
Outcomes	QALYs
Methods used to generate results	Cohort expected value analysis, Markov model
Health states	Alive and dead
Cycle length	3 months. The individual trial models are independent of the cycle length.
Transition from alive to dead	31/100,000 population per year. The same constant death rate is assumed for U300 and U100. The individual trial models are independent of the death rate.
Hypoglycaemic event rates	Rate of symptomatic and severe events from EDITION I, II and III
Costs	U300 or U100, mealtime insulin and treatment of severe hypoglycaemia events

Source: compiled during the evaluation

6.31 The key model drivers are summarised in the following table.

Table 6: Key drivers of the model

Description	Method/Value	Impact
Risk of hypoglycaemia with U100 (baseline risk)	Sourced from the EDITION I, II and III trials. Trial patients likely to have higher risk of events compared with PBS patients.	High, favours U300
Reduction in risk of hypoglycaemia with U300	Sourced from the EDITION I, II and III trials. Reduction not statistically significant for symptomatic events in EDITION I and II, and for severe events in the 3 trials.	High, favours U300
Disutility values for hypoglycaemia events	Values sourced from U100 March 2006 PBAC submission. In March 2006 the PBAC had a number of concerns regarding the utility values (see above) and data collected in the EDITION trials suggests no difference between the treatment groups in the perceived frequency of hypoglycaemia, fear of hypoglycaemia or health utility scores.	High, favours U300

Source: compiled during the evaluation

6.32 The results of the stepped economic evaluation are presented in the following table.

Table 7: Results of the stepped economic evaluation

Step and component	EDITION I			EDITION II			EDITION III		
	U300	U100	Increment	U300	U100	Increment	U300	U100	Increment
Step 1: trial-based costs and outcomes (6 month time horizon)									
Costs	$	$	$	$	$	$	$	$	$
Symptomatic + severe hypoglycaemia events	6.92	7.50	-0.58	3.09	4.09	0.99	1.04	1.89	0.85
Incremental cost/event avoided			$			$			$
Upper 95% CL of differences in outcome			Dominated			Dominated			$
Lower 95% CL of differences in outcome			$			$			$
Step 2: trial results and premodelling (extrapolation to 20 year time horizon, inclusion of cost of mealtime insulin (EDITION I), undiscounted)									
Costs	$	$	$	$	$	$	$	$	$
Symptomatic + severe hypoglycaemia events	276	299	-22.97	123	163	-39.50	42	75	33.74
Incremental cost/event avoided			$			$			$
Step 3: modelled evaluation (inclusion of cost for treating severe hypoglycaemic events, undiscounted)									
Costs	$	$	$	$	$	$	$	$	$
Symptomatic + severe hypoglycaemia events	276	299	-22.97	123	163	-39.50	42	75	33.74
Incremental cost/event avoided			$			$			$
Step 4: modelled evaluation (transformation to QALYs gained, discounted)									
Costs	$	$	$	$	$	$	$	$	$
QALYs									
Incremental cost/extra QALY gained			$			$			$
Step 5: modelled **evaluation (sequential model, EDITION III → EDITION II → EDITION I)**									
	Sequential model								
Costs	$	$	$						
QALYs									
Incremental cost/extra QALY gained			$						

Source: Table D.20, p179 of the submission; values in italics corrected during the evaluation.

6.33 The T2DM cost-effectiveness analysis was based on a reduction in symptomatic and severe hypoglycaemia. These were safety endpoints in the trials.

6.34 The difference between the U300 and U100 treatment groups in symptomatic events was not statistically significant in EDITION I and II. The lower event rate reduction with U300 in EDITION I (0.08) compared with EDITION II (0.24) and III (0.45) resulted in higher ICERs despite the higher baseline risk of events (EDITION I: 14.76; EDITION II: 8.11; EDITION III: 3.76 per patient year).

6.35 The difference in severe events was not statistically significant in any of the trials. The PSCR argued that the trials were not powered to detect a difference in these outcomes, but there was a consistent numeric reduction in events and thus the model accurately reflects the treatment benefits. The ESC remained concerned that by using the point estimates in the model, the base case essentially assumes that these are statistically significant and clinically meaningful differences. The sensitivity analyses in the evaluation using the upper 95% confidence intervals show that U300 could be dominated by U100. The PBAC considered the use of these non-statistically significant differences in the model to be problematic.

6.36 The results of univariate sensitivity analyses indicate that the model was also sensitive to the disutilities for fear of future symptomatic hyperglycaemic events. If

the disutility for fear of future symptomatic events was removed, for the EDITION I model U300 was dominated by U100 (i.e. is less effective and more costly), and for the EDITION II and III models the cost/QALY gained was $75,000/QALY - $105,000/QALY and more than $200,000/QALY, respectively.

6.37 As was the case in 2006, the disutility for fear of hypoglycaemia was a key driver of the model, with sensitivity analyses showing the ICERs for each trial dramatically changed with the removal of this disutility.

6.38 The PBAC considered that the fear of an event such as hypoglycaemia would be real, but the fear of having a particular event would exist for most conditions. Without clear evidence that treatment with the intervention would eliminate this fear, this is not a health state which should be modelled.

6.39 A biosimilar for insulin glargine 100 units/mL (Basaglar) was recommended for listing at the March 2015 PBAC meeting. Movement of insulin glargine 100 units/mL to the F2 formulary would trigger a 16% price cut. Reducing the price of U100 by 16% increases the cost/QALY gained to $75,000/QALY - $105,000/QALY for EDITION I, $15,000/QALY - $45,000/QALY for EDITION II and $15,000/QALY - $45,000/QALY for EDITION III.

6.40 The ESC proposed the following equi-effective doses in T2DM would be valid if the model was rejected and non-inferiority with U100 was accepted:

- Based on EDITION I: 103.29 units of U300 and 93.64 units of U100 i.e. 1 unit of U300 is equivalent to 0.91 units of U100
- Based on EDITION II: 91.02 units of U300 and 81.88 units of U100 i.e. 1 unit of U300 is equivalent to 0.90 units of U100
- Based on EDITION I: 59.37 units of U300 and 52.03 units of U100 i.e. 1 unit of U300 is equivalent to 0.88 units of U100.

6.41 The proposed price for U300 is based on [redacted]% use in T1DM and [redacted]% use in T2DM. The proportions are based on an analysis of the 10% PBS sample. Patients dispensed a basal insulin with a history of oral antidiabetic therapy were identified as T2DM patients whilst patients with no history of oral antidiabetic therapy were identified as being T1DM patients. Limited details of the analysis were provided and the reliability of the estimates could not be verified.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/year

6.42 Treatment with U300 is ongoing and doses are titrated based on blood glucose levels. The mean dose of U300 in the trials at 6 months ranged from 40 to 103 units. Assuming an average dose of 70 units, and [redacted]% use of the 5 pack of U300 and [redacted]% use of the 3 pack, the monthly and yearly cost of U300 is $[redacted] ($[redacted][1] x 30 x 70) and $[redacted] ($[redacted] x 365 x 70), respectively.

[1] Weighted dispensed unit cost = [redacted] x ([redacted]/[3 x 5 x 450]) + [redacted] x ([redacted]/[5 x 5 x 450]) = $[redacted]

6.43 The effective ex-manufacturer price for 25 x 300 unit pens of U100 is $[redacted] or $[redacted] per 300 unit pen. This is equivalent to $[redacted] per 450 units of insulin glargine.

- For T1DM a lower unit price is requested for U300 ($[redacted] per 450 units of insulin glargine). This is because of the requirement for an 18.6% higher unit dose with U300 compared with U100 (i.e. [redacted] x 1.186 = $[redacted]).
- For T2DM the same unit price is requested for U300. However, a 10.3-14.1% higher unit dose is required with U300 compared with U100. Adjusting for the higher dose, a premium of between $[redacted][2] ([redacted]%) and $[redacted][3] ([redacted]%) per pen (450 units) is requested for U300.

Estimated PBS usage & financial implications

6.44 This submission was not considered by DUSC. A market share approach with U300 replacing U100 was used in the submission.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
U100 prescriptions, 5 pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake T1DM/T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U300 prescriptions					
1 pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 pack	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS					
U300 net cost to PBS/RPBS (less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
U100 net cost offset to PBS/RPBS (less co-pay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table E.2, p188; Table E.4, p188, Table E.7, p189; Table E.13, p193; Table E.18, p194 of the submission; values in italics corrected during the evaluation.

The redacted table above shows that the estimated use and financial implications of U300 to the PBS/RPBS for the treatment of type 1 and type 2 diabetes is less than $10 million in years 1 and 2 and $10-20 million in years 3-5.

6.45 The submission estimated a net PBS/RPBS cost in year 5 of $10 - 20 million. This was likely to be an overestimate because the submission assumed 1 pack of U300 would replace 1 pack of U100, but on average a pack of U300 contains more units of insulin glargine. However, adjusting the pack equivalents ratio and simultaneously reducing the price of U100 by 16% resulted in a net PBS/RPBS cost in year 5 of $17-$26m. The net PBS/RPBS cost was also sensitive to the assumed growth of the insulin glargine market and the uptake of U300. Both the growth and uptake estimates used in the submission were uncertain.

6.46 The PBAC noted, at the revised cost-minimised price for T2DM, the net PBS/RPBS cost in year 5 would be less than the $10 - 20 million calculated by the submission.

[2] [redacted]-([redacted]/[redacted])
[3] [redacted]-([redacted]/[redacted])

Quality Use of Medicines

6.47 No information provided by the submission. However, as noted above, the unrestricted listing means the PBS population may be broader than the ACPM suggested indication, in adults, and the trial populations. The U300 pen is more concentrated than U100 cartridge/pen and there may be safety concerns, particularly with respect to use in children in T1DM.

7 PBAC Outcome

7.1 The PBAC recommended insulin glargine U300 as an unrestricted benefit on the basis of cost-minimisation to U100 for both T1DM and T2DM. The PBAC rejected the claimed benefit in hypoglycaemic events and the modelled cost effectiveness in T2DM. The PBAC noted the supportive comments from consumers but considered there was low clinical need for this additional formulation of insulin glargine.

7.2 The PBAC noted the unrestricted PBS listing could result in use in patient populations that are broader than the ACPM indication but did not consider the possibility of use outside the indication to be a significant issue.

7.3 The PBAC agreed that insulin glargine U100 was the appropriate comparator.

Type 1 diabetes

7.4 Based on the head-to-head trial EDITION IV, the PBAC accepted the claim of non-inferior efficacy and safety in patients with T1DM. For mean change in in HbA1c, the upper 95% confidence limit for the difference between the U300 and U100 treatment groups was below the 0.3%-0.4% non-inferiority margin previously used by the PBAC. The incidence of hypoglycaemia was similar with U300 and U100.

7.5 The PBAC accepted the estimated equi-effective dose of 1 unit of U300 being equivalent to 0.84 units of U100. The equi-effective dose was based on the mean dose at 6 months in EDITION IV. The equi-effective dose differed for morning versus evening dosing. For patients dosed in the morning, 1 unit of U300 was equivalent to 0.90 units of U100. For patients dosed in the evening, 1 unit of U300 was equivalent to 0.78 units of U100. In EDITION IV approximately 50% of patients were dosed in the evening and 50% in the morning. The PBAC noted that data on the relative proportions of patients dosing at different times of the day in Australian clinical practice are not available, but considered the 50% estimate to be conservative and favour the U300.

7.6 The PBAC considered the cost of mealtime insulin should have been included in the calculation for T1DM. At month 6 the mean daily mealtime insulin dose was higher for patients randomised to U300 compared with U100 (28.66 vs 27.11 units).

Type 2 diabetes

7.7 Based on three head-to-head trials (EDITION I, EDITION II and EDITION III) comparing U300 to U100 in T2DM, the PBAC accepted U300 as non-inferior to U100

in terms of comparative effectiveness but rejected the claim of superior comparative safety (reduced risk of hypoglycaemia) over U100 for T2DM.

7.8 For mean change in in HbA1c, the upper 95% confidence limit for the difference between the U300 and U100 treatment groups was below the 0.3%-0.4% non-inferiority margin previously used by the PBAC.

7.9 For the safety claim, the PBAC noted the statistically significant difference in the proportion of patients with at least one severe and/or confirmed nocturnal hypoglycaemic event between the start of week 9 and month 6, in the EDITION I and II trials. No statistically significant difference in this outcome was observed in EDITION III. The PBAC had several issues with the interpretation of these outcomes as superior safety:

- As noted by ACPM, the evening doses in the trials may have contributed to the incidence of nocturnal hypoglycaemia. The Committee noted that eTG stated: "There is some evidence to suggest that administering basal insulin in the morning is associated with less hypoglycaemia than evening dosing. Consider changing to morning administration if nocturnal hypoglycaemia becomes a problem."
- The incidence of hypoglycaemia in the trials may have been higher than in clinical practice due to a range of factors, including the aggressive glucose targets. The PBAC noted the arguments in the PSCR and Pre-PBAC response that the targets in the trials were higher than recommended in Australian clinical practice, but the attainment of these targets was balanced with the need to avoid hypoglycaemia. The PBAC disagreed that the trials enrolled patients with similar risk of hypoglycaemia as the Australian population.
- The definition of nocturnal events in the trials may not have captured what is considered a nocturnal event in practice, given the trial definition restricted these events to between 00:00 and 05:59 hours and nocturnal hypoglycaemia usually encompasses the night-time sleeping hours rather than restricting to a 6-hour window.
- There was no difference in the rates of documented symptomatic hypoglycaemia, per patient year, in EDITION I and II.
- There was no evidence of a difference in severe hypoglycemia (requiring assistance) in any of the three trials.

7.10 The PBAC did not accept U300 to have superior comparative safety in terms of reduced risk of hypoglycaemia.

7.11 The PBAC rejected the model in this submission, given a significant improvement in hypoglycaemia with U300 was not accepted and noting the issues with the 2006 model not addressed in this submission as outlined in paragraph 6.30.

7.12 Based on the acceptance of non-inferiority of both comparative clinical effectiveness and safety, the PBAC agreed with the following equi-effective doses for T2DM:

- EDITION I: 1U of U300 = 0.91U of U100
- EDITION II: 1U of U300 = 0.90U of U100
- EDITION III: 1U of U300 = 0.88U of U100

7.13 The PBAC noted the 28 day shelf life of the U300 and that the increase in the number of units per cartridge may result in increased wastage in a small group of patients. The PBAC considered a small reduction in the price of the U300 was appropriate to account for the potential wastage.

7.14 The PBAC advised that insulin glargine is suitable for prescribing by nurse practitioners.

7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Unrestricted listing.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
INSULIN GLARGINE injection, 300 international units/mL, 1 x 1.5 mL cartridge	1	1	Toujeo	Sanofi
INSULIN GLARGINE injection, 300 international units/mL, 3 x 1.5 mL cartridge	5	1	Toujeo	Sanofi
INSULIN GLARGINE injection, 300 international units/mL, 5 x 1.5 mL cartridge	5	1	Toujeo	Sanofi

9 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.

10 Sponsor's Comment

The sponsor had no comment.