

**7.06 INSULIN GLARGINE WITH LIXISENATIDE,  
 Injections (human analogue), cartridges, insulin  
 glargine 100 units per mL with lixisenatide 50  
 micrograms per mL, 3 mL, 5  
 Injections (human analogue), cartridges, insulin  
 glargine 100 units per mL with lixisenatide 33  
 micrograms per mL, 3 mL, 5  
 Soliqua<sup>®</sup>, sanofi-aventis Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The resubmission requested a Section 85 Authority Required (STREAMLINED) listing for insulin glargine with lixisenatide in a fixed ratio combination (FRC) for the treatment of adults with type 2 diabetes mellitus (T2DM). The PBAC previously considered insulin glargine with lixisenatide FRC at its March 2018 meeting.
- 1.2 The requested listing was based on a cost-minimisation analysis of insulin glargine with lixisenatide FRC given once daily compared to insulin glargine plus exenatide twice daily given separately.
- 1.3 Table 1 presents the key components of the clinical issue addressed by the resubmission.

**Table 1: Key components of the clinical issue addressed by the resubmission**

<b>Component</b>	<b>Description</b>
Population	Adults with Type 2 diabetes mellitus who have inadequate glycaemic control with basal insulin
Intervention	Insulin glargine with lixisenatide FRC administered once daily (plus metformin)
Comparator	Insulin glargine once daily and exenatide 5 to 10 mcg twice daily (plus metformin)
Outcomes	Glycaemic control, change in body weight, hypoglycaemic events, safety outcomes
Clinical claim	Non-inferior efficacy in terms of glycaemic control (HbA1c), and non-inferior safety in terms of treatment-emergent adverse events and hypoglycaemia, compared to insulin glargine plus exenatide 5 to 10 mcg twice daily

Source: Table 1.1.1, p21 of the resubmission  
 HbA1c, glycosylated haemoglobin

## 2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Max qty (packs)	Max qty (units)	No. of repeats	DPMQ	Proprietary name and manufacturer
100 units/mL insulin glargine + 50 mcg/mL lixisenatide 5 x 3 mL pre-filled pen ( <del>peach</del> )	1	5	5	\$ [REDACTED]	Sanofi-Aventis
100 units/mL insulin glargine + 33 mcg/mL lixisenatide 5 x 3 mL pre-filled pen ( <del>olive</del> )	1	5	5	\$ [REDACTED]	Sanofi-Aventis

Category/Program:	General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Diabetes mellitus type 2
PBS indication:	Diabetes mellitus Type 2
Treatment phase:	<del>Initial and continuing</del>
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p><i>The treatment must be in combination with metformin; OR</i></p> <p><i>Patient must have a contraindication to metformin; <del>The treatment must be in combination with metformin unless contraindicated or not tolerated;</del> AND</i></p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated;</p> <p>OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.</p>
Population criteria:	<del>Patient must be aged ≥18 years with diabetes mellitus type 2.</del>
Prescriber criteria:	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
Administrative Advice	<i>This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or an SGLT2 inhibitor.</i>

Source: Table 1.4.1 and 1.4.2, pp49-50 of the resubmission  
HbA1c, glycosylated haemoglobin; SGLT2, sodium-glucose co-transporter 2

- 2.1 Compared to the previous submission, the approved ex-manufacturer price per pen for insulin glargine 100 units/mL with lixisenatide 50 mcg/mL decreased by █████% from \$████ to \$████, and by █████% from \$████ to \$████ for insulin glargine 100 units/mL with lixisenatide 33 mcg/mL. Additionally, the maximum number of pens per script decreased from 25 pens in the previous submission to 5 pens in the resubmission. The proposed reduction in the maximum number of packs per prescription may potentially minimise wastage.
- 2.2 The requested restriction remained unchanged from the previous submission. The evaluation and the ESC considered this to be appropriate as the restriction aligned with the current PBS restriction for exenatide in combination with insulin.
- 2.3 The evaluation and the ESC noted that the requested PBS restriction was narrower than the TGA-approved indication, which allows use of insulin glargine with lixisenatide FRC along with metformin in patients inadequately controlled using metformin, metformin in combination with another oral agent or basal insulin with no definition for ‘inadequately controlled’ and no mention of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor.
- 2.4 The PBAC previously considered that use outside of the restriction was likely, including use in patients using other oral agents or basal insulin, patient’s naïve to insulin, through possible quadruple therapy use and use of doses higher than 60 mg insulin glargine equivalent per day (5.05 Insulin glargine with lixisenatide, March 2018 PSD, paragraph 2.6).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### **3 Background**

#### ***Registration status***

- 3.1 Insulin glargine with lixisenatide FRC was registered on the ARTG on 27 October 2017, and is indicated for use in combination with metformin for the treatment of adults with Type 2 diabetes mellitus to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose lowering medicinal product or with basal insulin. In its consideration of the previous submission, the ESC noted that the ARTG listing did not include a recommended dose for insulin glargine with lixisenatide FRC, which could suggest that a linear dose is acceptable, and the ESC further noted that the TGA recommended dose for lixisenatide as an add-on therapy is 20 mcg once daily for maintenance therapy.

**Previous PBAC consideration**

3.2 The previous (initial) submission for insulin glargine with lixisenatide FRC was considered by the PBAC at its March 2018 meeting. Outstanding matters of concern from the March 2018 meeting are summarised in Table 2.

**Table 2: Summary of outstanding matters of concern**

Component	Matter of concern	How the resubmission addresses it
Clinical claim	The ESC noted that other trials referenced in the TGA Product Information including the GetGoal X study may be informative in assessing effectiveness (6.12)	The resubmission argued that lixisenatide was non-inferior to exenatide based on results from GetGoal-X, however the evaluation noted that the results numerically favoured exenatide.
	The PBAC considered that a resubmission should provide further evidence to support the equi-effective doses (7.16)	
	The PBAC considered that non-inferiority was not demonstrated as the upper 95% CI exceeded the nominated non-inferiority margin of 0.3% to 0.4% (6.19, 7.6)	The resubmission argued that the PBAC previously accepted an upper 95% CI of 0.43% for dapagliflozin compared to insulin glargine at the March 2015 meeting. The evaluation and ESC considered that this may not be appropriate as the decision for dapagliflozin was related to total injection avoidance.
	The commentary noted that results of the matched adjusted indirect comparisons (MAIC) were not considered robust (6.28). The PBAC noted the limitations of the MAIC and acknowledged that Scenarios 2 and 3 resulted in an upper 95% CI of 0.36%, which was lower than the 0.4% non-inferiority margin but not the 0.3% margin (7.7)	No additional evidence was presented. The submission assumed that the PBAC had accepted non-inferiority and the literature search yielded no new evidence to present.
Economic evaluation	The commentary and the ESC stated the clinical claim of non-inferiority was not adequately supported (6.41, 6.42). The PBAC considered the claim of non-inferior comparative effectiveness to be uncertain but that it may be reasonable (6.43, 7.8) and on balance that a claim of non-inferior comparative safety was supported (6.44, 7.10)	No additional clinical evidence was presented other than the GetGoal-X results as supplementary information comparing lixisenatide and exenatide.
	The PBAC considered further evidence would be required to address the uncertainties associated with the claim of non-inferior comparative effectiveness (7.16)	
	The PBAC considered that the insulin-sparing effect claimed in the submission was not supported (6.16, 6.47, 7.9)	
Economic evaluation	The PBAC considered that capping of the dose in the LIXILAN-L trial to be a confounding factor in determining the equi-effective doses and that the proposed dose relativity was not supported (6.47, 6.53, 7.12)	No insulin sparing effect was assumed. The equi-effective doses were adjusted from: - 46.67 units/day insulin glargine and 16.87 mcg/day lixisenatide given as a FRC to 53.5 units/day and 19.3 mcg/day respectively, and from - 62.5 units/day insulin glargine and 19.3 mcg/day exenatide given separately to 53.5 units/day and 19.3 mcg/day respectively.
	The PBAC did not accept the equi-effective doses proposed in the submission and hence did not have a basis for determining the cost-effective price (7.14)	

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Component	Matter of concern	How the resubmission addresses it
	The PBAC considered that a difference in the dose relativities between lixisenatide and exenatide was not justified (6.47)	The newly proposed equi-effective doses in the resubmission suggest that lixisenatide and exenatide are non-inferior on a mcg to mcg basis, and the resubmission claimed the GetGoal-X results support this conclusion. This is inconsistent with PBAC's previous considerations of lixisenatide and exenatide.
	The commentary noted that the cost per unit of insulin glargine, and the cost per mcg of exenatide 5 mcg and 10 mcg were based on the price at first listing, and noted these costs could not be verified during the evaluation (6.48).	Current list prices for exenatide and insulin glargine were used in the resubmission.
Financial issues	In estimating regimens likely to be substituted, the submission excluded sulfonylureas, thiazolidinediones and acarbose from the analysis, which the PBAC considered may not be reasonable (6.63)	An allowance was made for substitution of sulfonylureas in Years 1 to 3.
	The PBAC considered there to be potential for use outside of the proposed restriction, which may increase the cost to government (6.67, 7.3, 7.15)	Not addressed.
	The PBAC considered there was a significant risk of wastage with the requested listing (6.67)	The resubmission proposed a smaller maximum quantity, which will help to address the wastage concern
	The PBAC noted that the assumed average insulin doses were based on clinical trial utilisation and may not reflect the average doses used in the Australian population (6.67)	The estimates assumed higher average insulin doses based on the newly proposed dose relativity. This may partly address this concern.
	The PBAC considered that there was potential for higher than forecast uptake due to convenience of regimen, and the reduction in patient co-payments compared to other treatments (6.67)	Uptake rates in the resubmission remained the same. With a lower maximum quantity requested, the concern regarding lower co-payments leading to higher uptake was considered to be less of a concern.
	The PBAC considered that a Risk Sharing Arrangement with an expenditure cap would be required for any resubmission (7.16)	Not addressed.
Quality use of medicines issues	A number of quality use of medicines issues were raised, with the PBAC noting the need for appropriate activities to be put in place (6.69, 6.71 – 6.74, 7.3)	No additional QUM activities were proposed.

All paragraph references refer to the 5.05 Insulin glargine with lixisenatide March 2018 PSD  
Source: 5.05 Insulin glargine with lixisenatide March 2018 PSD; Sections 2 to 4 of the resubmission

3.3 The PBAC considered a submission for lixisenatide for the treatment of Type 2 diabetes as dual therapy in combination with metformin, and as triple therapy in combination with metformin and a sulfonylurea, at the July 2014 PBAC meeting. The PBAC considered that for the dual therapy indication, the one head-to-head randomised trial comparing lixisenatide to exenatide in combination with metformin suggested that lixisenatide was statistically inferior compared to exenatide. The PBAC further considered that for the triple therapy indication, the indirect comparison did not provide conclusive evidence of non-inferiority of lixisenatide versus exenatide.

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

## 4 Population and disease

- 4.1 The resubmission did not change the clinical place of insulin glargine with lixisenatide FRC, positioning this as an option for patients who fail to achieve adequate glycaemic control with basal insulin. Alternative treatment intensification options included in the algorithm for patients who fail to achieve adequate glycaemic control with basal insulin are addition of a DPP4 inhibitor, an SGLT2 inhibitor, a GLP-1 agonist, rapid acting insulin, or switching to a premixed insulin. The PBAC previously agreed with the proposed clinical place for the product (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.3).

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

## 5 Comparator

- 5.1 The resubmission nominated basal insulin (insulin glargine) plus exenatide twice daily as the main comparator. This was the same comparator as the previous submission.
- 5.2 The PBAC previously agreed that the proposed comparator was appropriate, but also noted other therapies e.g. oral agents (sulfonylureas, DPP4 inhibitors, SGLT2 inhibitors), GLP-1 agonists and the addition of rapid-acting insulin or premixed insulin (in addition to basal insulin and metformin) may be displaced if insulin glargine with lixisenatide FRC were listed and therefore may be alternative comparators (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraphs 5.8 and 7.4).
- 5.3 The PBAC previously noted that 'Under the National Health Act 1953, the PBAC cannot make a positive recommendation for a medicine that is substantially more costly than an alternative therapy or therapies unless it is satisfied that the proposed medicine for some patients provides a significant improvement in efficacy or reduction in toxicity over the alternative therapy or therapies. Some of the identified alternative treatment options are likely to be less costly than insulin glargine plus exenatide (twice daily)' (5.05 Insulin glargine with lixisenatide FRC, March 2018 PBAC Meeting PSD paragraph 5.3).
- 5.4 The ESC agreed that the nominated comparator remained appropriate in the resubmission, and noted that there are several other potential comparators, particularly different insulin regimes, however it was difficult to determine which of these would be replaced in practice.
- 5.5 The ESC considered this treatment landscape is evolving and the main comparator may change with time despite the PBAC having previously accepted it. The Pre-PBAC Response acknowledged this, adding that 'in lieu of specific advice from the Department, the submission cannot reasonably be expected to anticipate future

entrants to the PBS for this indication, given that the market access strategies and timelines for competitors’ products are proprietary commercial information’.

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**

6.2 The PBAC noted and welcomed the input from individuals (1) via the Consumer Comments facility on the PBS website. The comment received described insulin glargine with lixisenatide as a promising alternative treatment for diabetic patients with reduced response to basal insulin alone.

### **Clinical trials**

6.3 Similar to the previous submission, this resubmission was based on an indirect comparison of insulin glargine with lixisenatide FRC to insulin glargine plus exenatide twice daily using insulin glargine only as the common reference. The indirect comparison was based on two head-to-head trials:

- Insulin glargine with lixisenatide FRC versus insulin glargine only (LIXILAN-L); and
- Insulin glargine plus exenatide twice daily versus insulin glargine only (GWCO).

6.4 The resubmission also provided data from the open-label, parallel-group, multicentre, randomised GetGoal-X trial (N=634), which had the primary objective of assessing safety and efficacy of lixisenatide 20 mcg once daily (n=318) to exenatide 10 mcg twice daily (n=316) in changing HbA1c from baseline to Week 24 in T2DM patients inadequately controlled (baseline HbA1c 7-10%) on metformin over a 24-week period. The resubmission did not critique the GetGoal-X trial, or provide any information on baseline demographics, or the risk of bias. GetGoal-X was not used to inform the indirect comparison, but included to support the resubmission’s contention that lixisenatide is non-inferior to exenatide.

6.5 Details of the trials presented in the resubmission are provided in Table 3.

**Table 3: Trials and associated reports presented in the resubmission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Indirect randomised trials</b>		
LIXILAN-L	A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with Type 2 diabetes mellitus (T2DM).	Clinical study report, 25 November 2015.

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Trial ID	Protocol title/ Publication title	Publication citation
	Aroda VR, Rosenstock J, Wysham C et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in Type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L Randomized Trial.	Diabetes Care 2016; 39(11):1972-1980.
	Wysham MD, Bonadonna RC, Aroda AR et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial.	Diabetes Obes Metab 2017; 19(10):1408-1415.
	Vidal J, Giorgino F, Stager W et al. Postprandial glycaemic outcomes of a fixed-ratio combination of insulin glargine and lixisenatide in the LixiLan-L trial.	Diabetologia 2016; 59 (Supp 1): S382-S383
	Aroda, VR, Rosenstock J, Wysham C et al. Erratum. Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial.	Diabetes Care 2016; 39:1972-1980. Diabetes Care 2017; 40(6): 809.
	The association between iGlarLixi and patient satisfaction with their treatment's ability to control type 2 diabetes is mediated by reduced glycaemic variability (GV) [Conference abstract].	Diabetologia 2017; 60 (Supp 1): S368.
	Characteristics and outcomes of type 2 diabetes patients titrated to 60U/day with insulin glargine/lixisenatide fixed-ratio combination vs insulin in LixiLan-L [Conference abstract].	Diabetologia 2017; 60 (Supp 1): S371.
	Blonde L, Bailey TS, Chao J et al. Characteristics and outcomes of type 2 diabetes patients titrated to 60U/day with insulin glargine/lixisenatide fixed-ratio combination vs insulin in LixiLan-L.	Diabetologia 2017; 60(1): S371.
	Dex T, Roborel De Climens A, Roberts M et al. The association between iGlarLixi and patient satisfaction with their treatment's ability to control type 2 diabetes is mediated by reduced glycaemic variability (GV).	Diabetologia 2017; 60(1): S368.
	Gaston-Mathe Y, Fan T, Shaunik A et al. Using machine learning algorithms to identify predictive factors of clinical outcomes with iGlarLixi or iGlar in the LixiLan-L trial [Conference abstract].	Diabetologia 2017; 60 (Supp 1): S373-S374.
	Giorgino F, Retnakaran R, Vidal J et al. iGlarlix effectively reduces residual hyperglycemia in patients with type 2 diabetes on basal insulin-a post-hoc analysis from the LixiLan-L study.	Diabetes 67: A292
	Giorgino F, Shaunik A, Liu M et al. The effect on lipid profiles of iGlarLixi versus iGlar in the LixiLan-L trial [Conference abstract].	Diabetologia 2017; 60 (Supp 1): S373.
	Niemoeller E, Souhami E, Wu Y et al. Iglarlix reduces A1C to a greater extent than basal insulin therapy regardless of A1C levels at screening.	Diabetes 2017; 66: A285.
	Niemoeller E, Souhami E, Wu Y et al. IglarLixi reduces HbA1c to a greater extent than basal insulin therapy regardless of HbA1c levels at screening [Conference abstract].	Diabetologia 2017; 60 (Supp 1): S370-S371.
	Niemoeller E, Souhami E, Wu Y et al. iGlarLixi Reduces Glycated Hemoglobin to a Greater Extent Than Basal Insulin Regardless of Levels at Screening: post Hoc Analysis of LixiLan-L.	Diabetes therapy 2018; 9(1): 373-382.
	Vidal J, Giorgino F, Stager W et al. Postprandial glycaemic outcomes of a fixed-ratio combination of insulin glargine and lixisenatide in the LixiLan-L trial [Conference abstract].	Diabetology and metabolic syndrome 2018; 10 (Supp 1): (no pagination).
	Wysham C, Bonadonna RC, Aroda VR et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial.	Diabetes Obes Metab 2017; 19(10): 1408-1415.
	Zisman A, Dex T, Roberts M et al. (2018). Bedtime-to-Morning Glucose Difference and iGlarLixi in Type 2 Diabetes: Post Hoc Analysis of LixiLan-L.	Diabetes Ther 2018.

Trial ID	Protocol title/ Publication title	Publication citation
GWCO	Buse JB, Bergenstal RM, Glass LC et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes.	Annals of Internal Medicine 2011; 154 (2): 103-112.
	Rosenstock J, Shenouda SK, Bergenstal RM et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimised insulin glargine in patients with type 2 diabetes.	Diabetes Care 2012; 35 (5):955-958.
	Wintle M, Pencek R, Han J et al. Addition of fixed-dose exenatide to insulin glargine therapy improved glycaemic control without increasing hypoglycaemia or weight gain across a range of insulin titration.	Diabetologia 2012; 55 (Supp. 1):S331
	Buse J, Glass L, Heilmann C et al. Weight change in placebo and exenatide (BID)-treated subjects with type 2 diabetes on insulin glargine: Effects of sex, diabetes duration, baseline A1C, and insulin dose. [Poster].	Diabetes 2011; 60 (Supp. 1):A266-A267.
	Bergenstal RM, Buse JB, Glass LC et al. Exenatide added to insulin glargine-treated patients with type 2 diabetes provided excellent fasting and postprandial control with weight loss and no increased risk of hypoglycaemia.	Diabetologia 2010; 53: S37.
	Buse JB, Han J, Miller S et al. Addition of exenatide BID to insulin glargine: A post-hoc analysis of the effect on glycemia and weight across a range of insulin titration.	Current Medical Research and Opinion 2014; 30(7):1209-1218.
GetGoal-X	Rosenstock J, Raccach D, Koranyi L et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study.	Diabetes Care 2013; 36:2945-51.

Source: Table 2.2.1, pp61-64 of the resubmission.

6.6 The key features of the trials included in the indirect comparison are summarised in Table 4. The Pre-Sub-Committee Response (PSCR) noted that the clinical analysis was largely unchanged because the updated literature search did not identify any new evidence, making the evidence presented the best available. The ESC noted that most of the clinical trial data remained the same as in the previous submission, and the ESC's views remained unchanged regarding these elements.

**Table 4: Key features of the included evidence for the indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Insulin glargine with lixisenatide FRC versus insulin glargine</b>					
LIXILAN-L	736	Randomised, active-controlled, open-label, parallel group, multi-centre trial (30-weeks with 6-week run-in phase).	High	Adults with Type 2 diabetes who have inadequate glycaemic control on basal insulin (15-40 units/day) and up to 2 OADs.	Change from baseline in HbA1c.
<b>Insulin glargine plus exenatide (twice daily) versus insulin glargine plus placebo</b>					
GWCO	259	Randomised, placebo-controlled, double-blind, parallel group, multi-centre trial (30-weeks).	Unclear	Adults with Type 2 diabetes who have inadequate glycaemic control on insulin glargine (≥20 units/day) +/- metformin +/- pioglitazone.	Change from baseline in HbA1c.

Source: Table 3 of the 5.05 Insulin glargine with lixisenatide FRC March 2018 PSD

FRC, fixed ratio combination; HbA1c, glycosylated haemoglobin, OAD, oral antidiabetic drugs, SMPG, self-monitored plasma glucose; FPG, fasting plasma glucose; EQ-5D, EuroQoL-5 dimensions-3 Levels; VAS, visual analogue scale; IWQoL-Lite, Impact of Weight on Quality of Life-Lite; TRIM-D, Treatment Related Impact Measure-Diabetes

### Comparative effectiveness

6.7 The results of an indirect comparison between insulin glargine with lixisenatide FRC and insulin glargine plus exenatide, using the common reference of insulin glargine presented in the resubmission were identical to the results presented in the previous submission, and these are summarised in Table 5. There was no statistically significant difference between the treatments for the primary outcome of change from baseline in HbA1c at 30 weeks or for patients reaching HbA1c targets of <7% or ≤6.5% at 30 weeks.

**Table 5: Indirect comparison of insulin glargine with lixisenatide FRC versus insulin glargine plus exenatide**

Trial	Insulin glargine with lixisenatide FRC	Common reference insulin glargine	Insulin glargine plus exenatide	Treatment difference (95% CI)
<b>Change from baseline in HbA1c at 30 weeks LSM (SE)</b>				
LIXILAN-L	-1.13% (0.06) N=364	-0.62% (0.06) N=364	-	-0.52% (-0.63, -0.40)
GWCO	-	-1.04% (NR) N=122	-1.74% (NR) N=137	-0.69% (-0.93, -0.46)
<b>Indirect WMD, 95% CI ( result &lt;0 favours FRC)</b>				<b>0.17% (-0.09, 0.43)</b>

Source: Table 2.6.4, p127 of the resubmission

HbA1c, glycosylated haemoglobin; LSM, least squares mean; SE, standard error; FRC, fixed ratio combination; CI, confidence interval; WMD, weighted mean difference

6.8 In its previous consideration of this analysis, the PBAC noted ‘there was no statistically significant difference between insulin glargine with lixisenatide FRC and insulin glargine plus exenatide for change from baseline in HbA1c at 30 weeks, with a weighted mean difference of 0.17% (95% CI: -0.09, 0.43), however as the upper 95% confidence limit exceeded the nominated non-inferiority margin of 0.3% to 0.4%, non-inferiority was not demonstrated’ (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.6).

6.9 The resubmission argued that the weighted mean difference of 0.17 for the change from baseline in HbA1c at 30 weeks was similar to the value of 0.16 (-0.11, 0.43) for dapagliflozin compared to insulin glargine that was considered at the March 2015 PBAC meeting. At that meeting, the PBAC accepted that dapagliflozin was non-inferior to insulin glargine despite the fact that it failed to meet the non-inferiority margin of 0.4%, stating that there was a clinical need for oral triple therapy to avoid injections (altogether), and also that the upper CI of 0.43 approached non-inferiority. Therefore, the resubmission argued that there is a precedent for listing an agent that reduces injections (in the case of insulin glargine with lixisenatide FRC, decreasing from three daily injections to one) and that the unadjusted analysis similarly approached non-inferiority. The evaluation considered that this precedent may not be relevant to insulin glargine with lixisenatide FRC as dapagliflozin was an oral therapy that allowed the patient to completely avoid injections, whereas insulin glargine with lixisenatide FRC is still a daily injection.

6.10 The PSCR stated that injection reduction is just as important, or possibly more

important, than injection avoidance. The ESC considered the previous consideration of dapagliflozin was not a suitable precedent for this current submission and considered there was a significant clinical difference between reducing injections from one to no injections compared to reducing from three injections to one.

- 6.11 Results from matched adjusted indirect comparisons (MAIC) for change in HbA1c from baseline at 30 weeks as well as the results of LIXILAN-L before matching, and the results from GWCO are presented in Table 6. The results (and the Scenario descriptions) were unchanged from the previous submission. Scenario 2 matched for variables interacting with the study treatment (treatment effect modifiers) that had different distributions across the trials and the resubmission relied upon this analysis for its clinical claim.
- 6.12 The ESC noted the MAIC analyses and reiterated its concerns regarding these analyses noted in the previous submission including the small number involved in the adjusted data from the LIXILAN-L study, the differences in trial design and populations, insulin dose capping in the LIXILAN-L trial and the statistically significant reduction in insulin glargine doses for patients in the GWCO trial using exenatide.

**Table 6: Results of the matched adjusted indirect comparisons for Scenario 2 and Scenario 3**

	Insulin glargine with lixisenatide FRC	Insulin glargine	Insulin glargine plus exenatide	Mean difference (95% CI)
<b>Change in HbA1c at 30 weeks</b>				
LIXILAN-L before matching	-1.12%(-1.21, -1.03)	-0.60%(-0.69, -0.51)	-	-0.52% (-0.65, -0.40)
LIXILAN-L Scenario 2	-1.11%(-1.21, -1.02)	-0.52%(-0.61, -0.42)	-	-0.60% (-0.73, -0.47)
LIXILAN-L Scenario 3	-1.13%(-1.22, -1.03)	-0.53%(-0.61, -0.44)	-	-0.60% (-0.73, -0.47)
GWCO	-	-1.04%(-1.22, -0.86)	-1.74%(-1.91, -1.56)	-0.69% (-0.93, -0.46)
<b>Indirect estimate Scenario 2 (Result &lt;0 favours FRC)</b>				<b>0.09 (-0.18, 0.36)</b>
<b>Indirect estimate Scenario 3 (Result &lt;0 favours FRC)</b>				<b>0.09 (-0.18, 0.36)</b>

Source: Table 2.6.9, p129 and Table 2.6.12, p133 of the resubmission; 5.05 Insulin glargine with lixisenatide FRC PSD Table 6

FRC, fixed ratio combination; CI, confidence interval; HbA1c, glycosylated haemoglobin

Scenario 2 matched for variables interacting with the study treatment (treatment effect modifiers) that had different distributions across the trials and this analysis was relied upon by the resubmission for their clinical claim

Scenario 3 matched for variables that interacted with the study treatment and had an impact on outcomes with different distributions between the trials

- 6.13 As for the previous submission, the resubmission proposed that the results of the MAIC analyses supported the claim of non-inferior efficacy given that the upper bound of the 95% CI was within the MCID of 0.4 most recently used by the PBAC. In relation to the previous submission, considering the limitations of the MAIC, the PBAC ‘acknowledged that for the outcome of change in HbA1c at Week 30, the matching undertaken (in Scenarios 2 and 3) resulted in an upper 95% confidence interval of 0.36% which was lower than the 0.4% non-inferiority margin, but not the 0.3% margin’ (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.7). The ESC considered that as per the original submission, the evidence presented did not support non-inferiority.
- 6.14 The ESC reiterated its previous advice that ‘... the dose of insulin was capped in the LIXILAN-L trial with 27% of participants reaching that cap, and that there was a

statistically significant reduction in insulin glargine doses for patients using exenatide in the GWCO trial which was not observed in the LIXILAN-L trial for patients using insulin glargine with lixisenatide.’ (5.05 Insulin glargine with lixisenatide PSD, March 2018 PBAC Meeting, paragraph 6.28). The ESC noted that for patients to get the recommended dose of lixisenatide of 20mcg they would require a 60 unit dose of insulin, and that many patients needing to down titrate the insulin dose to avoid hypoglycaemic events would not be receiving the therapeutic lixisenatide dose. The Pre-PBAC Response stated that patients whose glargine requirements exceed the amounts allowable by FRC would either not initiate therapy or would transition off therapy of insulin glargine with lixisenatide, and that those in the trial who reached the maximum glargine dose would have sought different treatment outside of the trial protocol. The sponsor posed that that this 27% of patients may explain some of the difference in efficacy between lixisenatide and exenatide.

- 6.15 The ESC also noted there was a lack of evidence to inform comparisons between the full dose of exenatide usually administered and partial doses of lixisenatide in the FRC product given the flexible insulin dosing in the trials. The Pre-PBAC Response stated that it was not appropriate to compare the doses of lixisenatide administered via the FRC in isolation without consideration of the insulin component, because, the impact of the FRC on accepted measures of disease control is driven by both components. The sponsor claimed that the MAIC was the best available evidence to compare the clinical effectiveness of insulin glargine with lixisenatide FRC to exenatide plus insulin glargine, because the MAIC study examined the most clinically relevant metric, HbA1c reduction (rather than insulin dose).
- 6.16 The resubmission also provided data from the open-label, parallel-group, multicentre, randomised GetGoal-X trial, which enrolled patients with T2DM inadequately controlled with metformin. Patients were randomised to receive either lixisenatide 20 mcg once daily (n=318) or exenatide 10 mcg twice daily (n=316), and change in HbA1c from baseline to Week 24 was measured. The trial reported a least squares (LS) mean difference of 0.17% (95% CI: 0.033, 0.297) in HbA1c change from baseline between the lixisenatide (-0.79%) and exenatide (-0.96%). The resubmission argued that as the treatment difference met the pre-defined non-inferiority margin of 0.4%, lixisenatide was non-inferior to exenatide. The evaluation noted that this may not be appropriate, as treatment with exenatide resulted in statistically significantly greater reduction in HbA1c from baseline than treatment with lixisenatide. This is also consistent with the PBAC’s comment in the previous submission that lixisenatide may be inferior to exenatide on a mcg to mcg basis (5.05 Insulin glargine with lixisenatide FRC, March 2018 PBAC Meeting PSD, paragraph 6.47). The PSCR stated that as a non-inferiority trial, the GetGoal-X trial tested only for non-inferiority, not superiority, and that it was not included in the main analysis due to differences in trial design and patient population. The ESC noted the results of the GetGoal-X trial and considered that it did not demonstrate non-inferiority of lixisenatide to exenatide as the exenatide

treatment arm saw a statistically significantly greater reduction in HbA1c from baseline than the lixisenatide arm.

### ***Comparative harms***

- 6.17 The resubmission did not present any new evidence relating to comparative safety. This was reasonable as the PBAC had previously considered that ‘on balance, ...insulin glargine with lixisenatide FRC was non-inferior in comparative safety to the comparator’ (5.05 Insulin glargine with lixisenatide FRC, March 2018 PBAC Meeting PSD, paragraph 6.44). As per its previous advice, the ESC noted that ‘... differences in methods for classifying adverse events made valid comparison difficult’, however it was noted fewer patients withdrew from the LIXILAN-L trial. The ESC considered that the higher number of withdrawals due to adverse events in the GWCO trial and the reduction in gastrointestinal (GI) adverse events in the LIXILAN-L trial may be due to the lower effective dose of lixisenatide administered compared to exenatide. The ESC also noted that a comparison of hypoglycaemia rates across studies was not possible due to the different definitions used (Insulin glargine with lixisenatide PSD, March 2018 PBAC Meeting, Paragraph 6.38). The ESC also considered there were no concerning toxicity signals, however there was a higher number of withdrawals due to adverse events in the GWCO trial.

### ***Interpretation of clinical evidence***

- 6.18 The resubmission described insulin glargine with lixisenatide FRC as non-inferior in effectiveness compared with insulin glargine plus exenatide and similar with respect to safety for the treatment of patients with T2DM who have received prior treatment with basal insulin with or without metformin and who have inadequate glycaemic control. The PSCR argued that PBAC previously agreed that non-inferiority may be reasonable and proceeded on the basis that non-inferiority had been accepted by PBAC. The ESC considered that this assumption may not be appropriate noting that PBAC previously concluded ‘non-inferior comparative effectiveness was uncertain, but may be reasonable’ (PSD, March 2018 PBAC Meeting, paragraph 7.8).
- 6.19 The resubmission maintained that insulin glargine with lixisenatide FRC may be better tolerated than insulin glargine plus exenatide in terms of gastrointestinal adverse events, including nausea and vomiting. However, the PBAC previously considered ‘the claim of reduced gastrointestinal adverse events was not adequately supported due to the reduced dose of lixisenatide compared with exenatide in the trials’ (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.10) and no additional data was provided with the resubmission to further support this claim. The ESC considered that the claimed reduction in nausea of lixisenatide to exenatide was not supported. The Pre-PBAC response reiterated the claim of the submission that

insulin glargine with lixisenatide exhibits superior clinical safety due to less GI adverse events

- 6.20 The PBAC previously considered the claim of non-inferior comparative effectiveness to be uncertain as the unadjusted indirect analysis did not meet the non-inferiority margin of 0.4%. However, the PBAC had considered that the claim may be reasonable given the key parameters which varied across the trials appeared to not be treatment effect modifiers and non-inferiority was demonstrated with a 0.4% margin using the MAIC analysis (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.8). Given that the main indirect comparison had not changed since the initial submission, and supplementary evidence from the GetGoal-X trial, indicated that treatment with exenatide resulted in statistically significantly greater HbA1c reduction compared to lixisenatide, the clinical claim remained uncertain. The ESC considered that as per the previous submission, the clinical claim of non-inferiority had not been demonstrated.
- 6.21 The Pre-PBAC Response argued that the submission presented the best available evidence in the absence of a head-to-head trial because the MAIC analysis met the 0.4% non-inferiority margin and appropriate measures were taken to reduce bias and heterogeneity. It stated that the ITC marginally missed the non-inferiority margin, however the analysis did not adjust for treatment effect modifiers, suggesting it may meet this margin had these been adjustments been included. It further added that GetGoal-X demonstrated similar HbA1c<7% results between exenatide and lixisenatide, and the non-inferiority margin was met, so on balance, non-inferiority was a reasonable conclusion.
- 6.22 In relation to safety, the PBAC previously considered that the claim of non-inferior comparative safety was reasonable (5.05 Insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 7.10).
- 6.23 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain, but considered that it may be reasonable.
- 6.24 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.25 Based on the claim of non-inferior efficacy and safety, a cost-minimisation analysis of insulin glargine with lixisenatide FRC versus insulin glargine plus exenatide twice daily was presented. The evaluation noted that this was only reasonable if the PBAC accepted the claim of non-inferior effectiveness and safety.
- 6.26 As the PBAC previously noted, some of the alternative therapies identified would be likely to be less costly than insulin glargine plus exenatide twice daily. The evaluation considered that a cost-minimisation against insulin glargine plus exenatide twice daily only did not represent a true cost-minimisation, and comparison against the least costly alternative therapies may have been more appropriate.

- 6.27 The resubmission used the following equi-effective doses in the cost-minimisation analysis:
- 53.5 units/day for insulin glargine and 19.3 mcg/day lixisenatide given as a fixed ratio combination, and
  - 53.5 units/day insulin glargine and 19.3 mcg/day exenatide given separately.
- 6.28 The doses were calculated based on the average dose of exenatide that was used by patients in the GWCO trial at 30 weeks of 19.3 mcg/day, a dose relativity of 1:1 for lixisenatide compared to exenatide, and calculation of the dose of insulin glargine required to deliver this dose per day in the FRC. The evaluation considered that this was likely optimistic as the PBAC had previously considered that lixisenatide may be inferior to exenatide on a mcg to mcg basis. This approach was considered more reasonable than the approach in the previous submission which assumed a dose relativity of 46.67 units/day insulin glargine and 16.87 mcg/day lixisenatide given as a fixed ratio combination, and 62.5 units/day insulin glargine and 19.3 mcg/day exenatide given separately. The PSCR stated that a 1:1 ratio for lixisenatide and exenatide was justified as there was no new literature identified making the original indirect trial comparison the best available evidence, and because the PBAC had previously accepted a claim of non-inferiority may be reasonable. The PSCR also stated that the GetGoal-X trial demonstrated non-inferiority as the upper CI did not exceed 0.4%. The ESC considered that the basis for determining a 1:1 ratio remained uncertain given there was no additional evidence was provided to support it. The Pre-PBAC Response stated that if there is a difference in efficacy between insulin glargine with lixisenatide and insulin glargine and exenatide, it is unlikely to be of a clinically relevant magnitude given the available evidence and accepted MCID and non-inferiority margins in the disease area. The sponsor added that it was unclear how the 1:1 lixisenatide to exenatide ratio could be appropriately adjusted to take account of a potential difference in HbA1c reduction between treatments that does not meet accepted measure of clinical relevance and is unlikely to result in a difference in patient-relevant outcomes.
- 6.29 Table 7 summarises the steps used to calculate the total daily cost of insulin glargine plus exenatide twice daily used in the cost minimisation analysis.

Table 7: Derivation of price per day of insulin glargine plus exenatide (twice daily)

	Insulin glargine + exenatide twice daily	Insulin glargine with lixisenatide FRC
<b>Insulin glargine</b>		
AEMP per pack (effective price)	\$█/pack	\$█/pack
Units per pack (5 pens)	1500 units/pack	1500 units/pack
Price per unit (\$█/1500 units)	\$█/unit	\$█/unit
Price of 53.5 units (GWCO Week 30)	\$█	\$█
<b>Exenatide 10 mcg</b>		
AEMP per pack	\$72.96/pack	-
Micrograms per pack	600 mcg/pack	-
Price per mcg (\$72.96/600 mcg)	\$0.122/mcg	-
<b>Exenatide 5 mcg</b>		
Exenatide 5 mcg AEMP per pack	\$51.07/pack	-
Micrograms per pack	300 mcg/pack	-
Price per mcg (\$51.07/300 mcg)	\$0.17/mcg	-
<b>Weighted price/unit to achieve GWCO Week 30 dose (19.3 mcg) GLP-1 agonists</b>		
Exenatide 10 mcg (93% x 0.122/mcg)	\$0.125/mcg at 19.3mcg	-
Exenatide 5 mcg (7% x 0.17/mcg)		
Lixisenatide 19.3mcg	-	\$0.125/mcg at 19.3mcg
Weighted price of 19.3 mcg	\$2.41	\$2.41
<b>Needle costs</b>		
Cost per pack of 100 needles <sup>1</sup>	\$31.93	\$31.93
Cost per needle	\$0.319/needle	\$0.319/needle
Total needles assumed	2 needles/day: \$0.639	1 needle/day: \$0.319
Offset claimed (50% of total needle reduction)	-	\$0.319
<b>Total daily cost</b>		
Insulin glargine (\$█) + exenatide weighted (\$2.41) + needles (\$0.639)	\$█	-
Insulin glargine (\$█) + lixisenatide (\$2.41) + needles (\$0.32) + needle offset (\$0.32)	-	\$█

Source: 'iGlarLixi CMA November 2018' Excel workbook, Attachment 9 of the resubmission

AEMP, approved ex-manufacturer price, FRC = fixed ratio combination, GLP-1 = Glucagon-like peptide -1

<sup>1</sup> <http://www.pharmacydirect.com.au/product/bd-micro-fine-29g-x-127mm-pen-needle-box-100-037951.aspx> [accessed 21 September 2017 and checked still current price at 19 November 2018]

- 6.30 The resubmission derived the cost per unit of insulin glargine, and the cost per mcg of exenatide 5 mcg and 10 mcg based on the current PBS approved ex-manufacturer prices. This differed from the approach taken in the previous submission, which used the price for each drug when first listed. The resubmission's revised approach was appropriate.
- 6.31 The cost of treatment per day was derived using the equi-effective doses, and assuming █% use of exenatide 5 mcg and █% use of exenatide 10 mcg, based on the weighting required to achieve a dose of 19.3 mcg/day.
- 6.32 Table 8 summarises the steps used to derive the requested ex-manufacturer price for each strength of insulin glargine with lixisenatide FRC pen.

**Table 8: Derivation of the AEMP for insulin glargine with lixisenatide FRC**

	Insulin glargine			Lixisenatide			Cost offset from needles	Requested AEMP/pen	Requested AEMP/pack	Expected use
	IU	Cost/IU <sup>1</sup>	Cost/pen	Mcg	Cost/mcg <sup>2</sup>	Cost/pen				
2 units/1 mcg	300	\$████	\$████	150	\$████	\$████	\$████ <sup>3</sup>	\$████	\$████	██%
3 units/1 mcg	300	\$████	\$████	100	\$████	\$████	\$████ <sup>4</sup>	\$████	\$████	██%
<b>Weighted mean</b>								\$████	\$████	100%

<sup>1</sup> Same as price per unit insulin glargine Table 3.4.1

<sup>2</sup> Same as weighted price/unit exenatide to achieve GWCO Week 30 dose (19.3 mcg), Table 3.4.1

<sup>3</sup> Resubmission assumed █████ needles saved per pen based on lixisenatide daily dose of 19.3mcg/day

<sup>4</sup> Resubmission assumed █████ needles saved per pen based on lixisenatide daily dose of 19.3mcg/day

Source: 'iGlarLixi CMA November 2018' Excel workbook, Attachment 9 of the resubmission AEMP, approved ex-manufacturer price; IU, international unit

- 6.33 The calculated AEMP per pack equated to the requested DPMQs of \$████ for the 2 unit/1 mcg pack of five pens and \$████ for the 3 unit/1 mcg pack of five pens.
- 6.34 Compared to the previous submission, the following changes were made to the cost-minimisation analysis: the assumed insulin sparing effect was removed in line with the PBAC's advice (5.05 Insulin glargine with lixisenatide, FRC March 2018 PBAC Meeting PSD, paragraph 6.47), and the dose relativity of lixisenatide and exenatide was assumed to be 1:1. Additionally, prices at first PBS listing were no longer used, and the requested maximum number of packs was reduced to one.
- 6.35 These changes resulted in a reduction in the cost per day for insulin glargine plus exenatide twice daily and insulin glargine with lixisenatide FRC from \$████ in the previous submission to \$████ in the resubmission, and a corresponding decrease in the approved ex-manufacturer price per pen for insulin glargine 100 units/mL lixisenatide 50 mcg/mL by 38.8% from \$████ to \$████, and by █████% from \$████ to \$████ for insulin glargine 100 units/mL lixisenatide 33 mcg/mL.

**Drug cost/patient/year:**

- 6.36 \$████ (3 units/1 mcg pen) and \$████ (2 units/1 mcg pen); assuming:
- 3 units/1 mcg pen: At the requested DPMQ of \$████ for five pens (300 units/100 mcg insulin glargine/lixisenatide per pen), assuming 14.1 scripts per year (based on 57.9 units/19.3 mcg per day), the price per patient per year is \$████.
  - 2 units/1 mcg pen: At the requested DPMQ of \$████ for five pens (300 units/150 mcg insulin glargine/lixisenatide per pen), assuming 9.4 scripts per year (based on 38.6 units/19.3 mcg per day), the price per patient per year is \$████.
- 6.37 The differences in the number of scripts assumed for each FRC was due to the difference in the lixisenatide content in each type of pen, with a higher number of

pens/scripts required to administer an average daily dose of 19.3 mcg of lixisenatide in the 2:1 FRC compared to the 3:1 FRC.

### **Estimated PBS usage & financial implications**

- 6.38 The resubmission was not considered by DUSC.
- 6.39 Compared to the previous submission, the resubmission made the following changes to the financial estimates:
- An allowance was made for uptake of the product in patients who would otherwise have been prescribed basal insulin plus a sulfonylurea (glipizide, glimepiride, gliclazide and glibenclamide) in Years 1 to 3. (The addition of thiazolidinedione to basal insulin was considered but not included due to minimal use. The addition of acarbose to basal insulin was not included);
  - A minor mistake regarding the metformin co-payment was corrected;
  - More recent data from a 10% sample of PBS data including first and second quarter data from 2018 was used to estimate the eligible patient population and the expected patient co-payments; and
  - The new requested DPMQ for insulin glargine with lixisenatide FRC was used and the DPMQ of comparator drugs was updated. The prices of exenatide and insulin glargine were no longer based on their prices at the time of first listing.
- 6.40 The PSCR stated that potential patients for insulin glargine with lixisenatide are unlikely to choose any other option making it inappropriate to include other treatment options in the cost minimisation analysis. The ESC noted that the estimates presented in the resubmission assumed substitution from a range of therapies which did not align with this statement.
- 6.41 Table 9 presents the estimated utilisation and financial impact of insulin glargine with lixisenatide FRC over the first six years of listing.
- 6.42 The resubmission estimated a net cost to the PBS in Year 6 of less than \$10 million. The estimated cumulative net cost over six years was \$30 to \$60 million. This was lower than the estimated net cost in the previous submission (less than \$10 million in year 6 of listing and cumulative net cost over first six years of listing of \$30 to \$60 million). The additional cost from insulin glargine with lixisenatide FRC listing was due to the requested price for insulin glargine being greater than the therapies substituted for.
- 6.43 In relation to the previous submission, DUSC considered that the estimated eligible patient population was probably reasonable, however DUSC also noted that there is potential for use outside of the proposed restriction, particularly in patients who are insulin naïve with inadequate glycaemic control on oral medications, or on GLP-1 agonists +/- oral medications, which may increase the cost to the Government (5.05 insulin glargine with lixisenatide, March 2018 PBAC Meeting PSD, paragraph 6.67). This was not addressed in the resubmission.

- 6.44 The Pre-PBAC response stated that ‘Given that the (insulin glargine with lixisenatide) FRC includes insulin, there is less potential for use outside the reimbursed restriction compared with exenatide because use of GLP-1 receptor agonist monotherapy is not possible ... the sponsor contends that the potential for use outside the proposed restriction is low.’

**Table 9: Total utilisation and cost to the PBS of listing insulin glargine with lixisenatide FRC**

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
<b>Estimated eligible population</b>						
Total						
<b>Estimated displaced scripts</b>						
Basal insulin + exenatide						
Basal insulin + DPP4						
Basal insulin + SGLT2						
Basal + rapid insulin						
Premixed insulin						
Basal insulin + SU						
Total FRC patients						
Previous submission: total FRC patients 2018-2023						
<b>Total cost of listing insulin glargine with lixisenatide FRC (2 units/1 mcg: 22.8%; 3 units/1 mcg: 77.2%)</b>						
Total FRC scripts <sup>1</sup>						
Additional metformin scripts <sup>2</sup>						
Cost to PBS <sup>3</sup>	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Displaced scripts</b>						
Cost to PBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Net changes to the PBS/RPBS</b>						
<b>Net cost to PBS/RPBS (less co-payments)</b>	\$	\$4	\$	\$	\$	\$
Previous submission: Net cost to PBS (less co-payments) 2018-2023	\$	\$	\$	\$	\$	\$
Previous submission with correct metformin co-payment: Net cost to PBS (less co-payments) 2018-2023	\$	\$	\$	\$	\$	\$

Source: Table 4.3.2, p160; Table 4.3.4, pp162-163; Table 4.3.5, p164; Table 4.3.6, p165; Table 4.3.7, p166; Table 4.3.10, p169; Tables 4.4.1 – 4.4.7, p172; Table 4.5.1, pp173-174; Table 4.6.3, p176 of the resubmission

BD= Twice daily; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter 2; FRC, fixed ratio combination; SU, sulfonylurea; TZD, thiazolidinedione; NA, not applicable

<sup>1</sup> Assume 22.8% use 2:1 insulin glargine with lixisenatide FRC (Peach) at 9.4 scripts per year and 77.2% use 3:1 insulin glargine with lixisenatide FRC (Olive) at 14.1 scripts per year

<sup>2</sup> Assume 65% of all patients treated with basal insulin + DPP4 and 17% of patients treated with basal insulin+SGLT2 were treated with metformin as part of a fixed dose combination, therefore requiring additional metformin scrips when switching to insulin glargine with lixisenatide FRC, at 11.9 packs per year.

<sup>3</sup> Includes cost of additional metformin

The redacted table shows that at Year 6, the estimated number of patients was 10,000 to 50,000.

- 6.45 The following issues identified in the evaluation of the previous submission were considered to remain of concern in the resubmission:
- Uptakes rates were considered to be uncertain and not consistent with data presented from the survey of endocrinologists. Uptake rates may be higher than estimated due to the convenience of a once daily subcutaneous injection.
  - Insulin glargine with lixisenatide FRC may also be used in a proportion of patients who would otherwise have been treated with insulin up-titration, and this was not accounted for. The PSCR stated that this was unlikely as patients would have already tried this or found it to not be a reasonable option.
  - There was an assumption that the only PBS-listed basal insulin that would be replaced in clinical practice would be insulin glargine. However, patients using isophane insulin (intermediate-acting basal insulin) would also be eligible for insulin glargine with lixisenatide. Exclusion of intermediate basal insulins from the analysis may have underestimated the number of eligible patients. The PSCR considered replacement of isophane insulin would not have any impact on financial projections.
  - The large treatment coverage periods used in the analysis for the 10% Medicare sample are likely to have overestimated co-administration and underestimated treatment switching and discontinuations.
  - Despite claiming that insulin glargine with lixisenatide FRC would improve treatment adherence, the resubmission did not adjust for differences in treatment adherence.
- 6.46 The ESC considered many of the same concerns regarding utilisation and financial estimates applied to the resubmission, including those around uptake rates and dosing issues associated with the FRC.

### ***Quality Use of Medicines***

- 6.47 No additional information was provided in the resubmission on quality use of medicines. The same quality use of medicines issues detailed in the previous submission, the commentary on the previous submission and advice from DUSC continue to be relevant for the resubmission. Namely:
- Correct administration of insulin glargine with lixisenatide FRC, prevention of medication errors, and the appropriate storage, handling and disposal of insulin glargine with lixisenatide FRC.
  - Loss of glycaemic control during the switch to insulin glargine with lixisenatide FRC and when patients who reach the maximum dose switch to an alternate therapy.
  - Loss of treatment flexibility as the lixisenatide dose is dependent on the basal insulin requirements. Patients may receive lower than recommended doses of lixisenatide and may not obtain the full benefit of GLP-1 agonist therapy.
  - Potential for patients requiring insulin doses >60 units to administer higher than recommended doses (i.e. through multiple injections of the FRC) resulting in exposure to higher than recommended doses of lixisenatide.
  - Risk of intentional or inadvertent quadruple therapy.

- Concurrent adjustment of insulin glargine and lixisenatide dosage may make it difficult to determine which component is responsible for adverse events.
- 6.48 At its March 2018 meeting, the PBAC noted the quality use of medicines issues identified above and noted the need for appropriate activities to be put in place (5.05 insulin glargine with lixisenatide FRC, March 2018 PBAC Meeting PSD, paragraph 6.74).
- 6.49 The Pre-PBAC Response to this outstanding issue stated the sponsor is ‘willing work with the Department to ensure that mechanisms are in place to help guide physicians towards appropriate patient selection...’.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of insulin glargine with lixisenatide fixed ratio combination (FRC) for treatment of adults with type 2 diabetes mellitus who have inadequate glycaemic control with basal insulin on the basis that the proposed price was unacceptably high given the residual uncertainty around the claim of non-inferiority and the appropriate equi-effective doses. The PBAC considered that on balance, cost-effectiveness had not been demonstrated and noted that there was no strong clinical need for insulin glargine with lixisenatide due to other PBS listed treatment options.
- 7.2 The PBAC acknowledged there may be practical benefits for some patients in reducing the number of daily injections from three to one, however also considered there may be disadvantages to some patients due to reduced flexibility of insulin glargine dosing and the potential inferiority of lixisenatide compared to exenatide.
- 7.3 The PBAC considered that the reduction in maximum quantity from 5 packs to 1 in the resubmission was appropriate to address its March 2018 concerns regarding wastage and potential for higher than forecast uptake due to convenience. The PBAC recalled that at that time it had also raised concerns regarding use outside of the proposed restriction and that this had not been addressed in the resubmission.
- 7.4 The PBAC reiterated its March 2018 advice that the proposed clinical place for the product was reasonable.
- 7.5 The PBAC considered that the comparator proposed by the submission remained appropriate.
- 7.6 The PBAC noted the additional evidence from the GetGoal-X trial comparing exenatide to lixisenatide (without insulin glargine) presented in the resubmission, and considered that this did not reduce the uncertainty in relation to comparative clinical effectiveness. This was because the results demonstrated a statistically significantly larger reduction in HbA1c for exenatide compared to lixisenatide which did not support non-inferiority, and the results were of limited applicability as the treatment arms of the trial did not include insulin glargine.

- 7.7 Overall, as no additional clinical data was presented in the resubmission to support the claim of non-inferiority of insulin glargine with lixisenatide FRC compared to insulin glargine with exenatide, the PBAC reiterated its March 2018 advice that the claim of non-inferior comparative effectiveness was uncertain but may be reasonable.
- 7.8 The PBAC reiterated its March 2018 advice that the claim of lixisenatide exhibited less gastrointestinal adverse events when compared to exenatide was not adequately supported. The PBAC considered that the claim of non-inferior safety of insulin glargine with lixisenatide to the comparator was reasonable.
- 7.9 The PBAC noted the insulin sparing-effect claimed in the March 2018 submission had been removed in the resubmission which aligned with the previous PBAC advice, and that equi-effective doses had been adjusted to a one-to-one ratio (53.5 units/day for insulin glargine and 19.3 mcg/day lixisenatide given as a fixed ratio combination equi-effective to 53.5 units/day insulin glargine and 19.3 mcg/day exenatide given separately). The PBAC considered the revised equi-effective ratio may remain optimistic, as the PBAC had previously considered lixisenatide may be inferior to exenatide on a mcg to mcg basis (5.9 Lixisenatide Dual Triple Therapy , July 2014 PBAC Meeting PSD paragraph 7.5). The PBAC further considered that the patients on insulin glargine with lixisenatide FRC may not receive the therapeutic dose of lixisenatide (20 mcg daily) due to the need to down titrate the insulin component in the FRC formulation, which increased uncertainty around equi-effective doses.
- 7.10 The PBAC noted adjustments to the estimated use to allow for uptake of the product in patients that would otherwise have been prescribed basal insulin plus a sulfonylurea in years 1 to 3 and the use of more recent PBS sample data to estimate the eligible patient population and co-payments and correction to use current PBS prices. The PBAC recalled its March 2018 advice that the eligible population figures were acceptable for the proposed population, however utilisation was likely underestimated due to probable use outside of the restriction, preferences for fewer injections and lower out of pocket costs for consumers. The PBAC considered that these concerns were partially addressed in the resubmission through the use of revised PBS data samples, and revisions to the maximum quantities in the restriction.
- 7.11 The PBAC noted the changes to the equi-effective doses resulted in lower proposed ex-manufacturer prices for both the 50 mcg/mL and 33 mcg/mL pens, and a reduction of less than \$10 million over 6 years compared to the previous submission. The PBAC noted that there remained a proposed net increased cost to PBS of \$30 to \$60 million over 6 years. Considering the small potential benefit to patients of reducing from three injections to one injection weighed against disadvantages of reduced dosing flexibility and possible inferiority of lixisenatide compared to exenatide, the PBAC did not consider that this increased cost to the PBS was adequately justified.
- 7.12 The PBAC noted that no quality use of medicine activities were proposed in the resubmission, as previously requested by the PBAC.

- 7.13 The PBAC noted the resubmission did not propose a Risk Sharing Arrangement (RSA) with an expenditure cap, which was recommended in the March 2018 consideration (5.05 Insulin glargine with lixisenatide March 2018 PBAC Meeting Public Summary Document (PSD), paragraph 7.16). It noted the Pre-PBAC response stated (the Sponsor) 'is willing to work with the Department to ensure that mechanisms are in place to help guide physicians towards appropriate patient selection and to provide the Commonwealth with budgetary certainty', however did not explicitly express willingness to negotiate an RSA. The PBAC considered that a RSA subsidy cap set at an acceptable utilisation rate of eligible patients with a 100% reimbursement rate for use over the subsidy cap would be appropriate to provide the Commonwealth with a degree of budgetary certainty.
- 7.14 The PBAC considered that in the absence of further data to support a major submission, a future resubmission may be acceptable as a minor submission. The PBAC considered that in light of the evidence presented, a proposal for PBS listing should be at no net cost to the PBS given insulin glargine with lixisenatide FRC was optimistically considered non-inferior to the comparator, however was likely inferior, and therefore did not justify increased PBS expenditure. A price reduction was considered to be appropriate to address the residual uncertainty around the claim of non-inferiority and the appropriate equi-effective doses. A resubmission would need to include a RSA with an expenditure cap as outlined above to mitigate residual risk due to uncertain drug utilisation from use outside of the restriction, preferences for fewer injections and lower out of pocket costs for consumers. The PBAC considered that there was unlikely to be any additional evidence to support the claim of non-inferiority of lixisenatide to exenatide, and that this approach to a minor submission could pragmatically support the listing of insulin glargine with lixisenatide FRC, at a price reflective of available evidence.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 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.

## **9 Sponsor's Comment**

Sanofi is disappointed by the Committee's decision and the further delay to access to a convenient alternative treatment option for Australian diabetics in provided by the fixed ratio combination of lixisenatide with insulin glargine. We welcome the Committee's pragmatism and hope to be able to find a way forward towards providing access to this medicine in Australia.