

5.05 INSULIN GLARGINE WITH LIXISENATIDE

Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 50 microgram per mL, 3 mL, 5 Injections (human analogue), cartridges, insulin glargine 100 units per mL with lixisenatide 33 microgram per mL, 3 mL, 5 Soliqua®

Sanofi-Aventis

1 Purpose of Application

- 1.1 The submission requested a Section 85, Authority Required (STREAMLINED) listing for insulin glargine with lixisenatide fixed ratio combination (FRC) for the treatment of patients with Type 2 diabetes mellitus who have inadequate glycaemic control with basal insulin. The PBAC has not previously considered insulin glargine with lixisenatide FRC.
- 1.2 The listing was requested on a cost-minimisation basis compared to insulin glargine plus exenatide (twice daily).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with Type 2 diabetes mellitus who have inadequate glycaemic control with basal insulin.
Intervention	Fixed ratio combination of insulin glargine with lixisenatide 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, p.2 of the submission

Abbreviations: 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.

Public Summary Document– March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
INSULIN GLARGINE WITH LIXISENATIDE				Soliqua® Sanofi-aventis Australia Pty Ltd
100 units/mL insulin glargine with 50 mcg/mL lixisenatide, 5x 3 mL pre-filled peach pen	5	1	\$ [REDACTED]	
100 units/mL insulin glargine with 33 mcg/mL lixisenatide, 5x 3 mL pre-filled olive pen	5	1	\$ [REDACTED]	

Category / Program	GENERAL – General Schedule (Code GE)
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:	Initial and continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with metformin unless contraindicated or not tolerated
Clinical criteria:	<i>The treatment must be in combination with metformin; OR</i> <i>Patient must have a contraindication to metformin;</i> <i>AND</i> 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; OR 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>Prescriber Instructions</p>	<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>
<p>Administrative Advice</p>	<p><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></p>

- 2.1 The proposed PBS restriction was identical to the current PBS restriction for exenatide (twice daily) in combination with insulin, apart from the removal of the statement that 'the treatment must be in combination with insulin'.
- 2.2 The requested PBS restriction is narrower than the TGA-approved indication, which allows use in patients inadequately controlled using metformin, metformin in combination with another oral agent or basal insulin. The ESC noted this difference and considered that there was the potential for use outside the proposed PBS restriction.
- 2.3 The proposed PBS restriction is complex and may be able to be simplified.
- 2.4 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 a GLP-1 agonist (+/- oral medications). The ESC considered that PBS restrictions currently require patients to discontinue dipeptidyl peptidase-4 inhibitors (DPP-4), sodium-glucose co-transporter-2 (SGLT-2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1) prior to initiating basal insulin, and that these can be added post basal insulin initiation if HbA1c remains above 7%. The ESC noted that combinations of DPP-4, SGLT-2 and GLP-1 products are not currently reimbursed under the PBS. The ESC advised that there was a risk of use by patients who continue to use gliptins, glitazones, GLP-1 or SGLT2 inhibitors as well as the FRC under the proposed restriction wording.
- 2.5 The DUSC interpreted the proposed restriction to only require that a patient was uncontrolled prior to initiation of the third therapy and that switching from an

existing triple therapy (e.g. insulin + metformin + gliptin or glitazone or exenatide or SGLT2 inhibitor) for reasons other than inadequate control would be permissible.

- 2.6 The PBAC considered that use outside of the restriction was likely, including to patients using other oral agents or basal insulin, patients naïve to insulin, through possible quadruple therapy use and use of doses higher than 60mg insulin glargine equivalent per day.

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. The ESC noted that the ARTG listing does not include a recommended dose for insulin glargine with lixisenatide which could suggest that a linear dose is acceptable. The ESC noted that the TGA recommended dose for lixisenatide as an add-on therapy is 10-20mcg once daily.

Previous PBAC consideration

- 3.2 The PBAC considered a submission for lixisenatide for the treatment of Type 2 diabetes in combination with insulin at the July 2014 PBAC meeting. The submission was rejected on the basis that the clinical place of glucagon-like peptide-1 drugs in Type 2 diabetic patients requiring insulin therapy was yet to be established, and the appropriate comparator was not only titrated insulin. The PBAC also did not accept the clinical equivalence of lixisenatide to basal-bolus or premixed insulin regimens as this claim relied on complex series of indirect analyses that reduced the reliability of the results.
- 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.

- 3.4 In its consideration of both submissions in 2014, the PBAC considered that any future resubmissions would need to particularly address claims regarding lixisenatide's comparative efficacy and safety compared to exenatide (twice daily), and would need to establish a compelling clinical need for lixisenatide therapy if non-inferiority to existing therapy could not be conclusively demonstrated in a major resubmission (Lixisenatide Public Summary Document, July 2014).
- 3.5 The PBAC considered a submission for exenatide twice daily for the treatment of Type 2 diabetes in combination with insulin at the March 2015 PBAC meeting. The submission was recommended on a cost analysis basis compared with intensification of insulin therapy to the full basal-bolus regimen.

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

4 Population and disease

- 4.1 The submission noted that around 85-90% of the estimated 1.7 million Australians with diabetes mellitus have Type 2 diabetes, and that a further 2 million Australians are at high risk of developing Type 2 diabetes (Diabetes Australia, 2015). The submission further noted that diabetes mellitus is associated with significant health, social, and economic impacts. Long-term consequences of poor glycaemic control include microvascular complications (retinopathy, nephropathy, neuropathy), macrovascular complications (cardiovascular disease, cerebrovascular disease) reduced quality of life, and premature mortality. The risk of microvascular and macrovascular complications is related to the frequency, duration and severity of hyperglycaemia.
- 4.2 The submission positioned insulin glargine with lixisenatide FRC 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.

5 Comparator

- 5.1 The submission nominated basal insulin (insulin glargine) plus exenatide twice daily as the main comparator. The main arguments provided in support of this nomination were:
 - Insulin glargine is the only basal insulin currently listed on the PBS for use in Type 2 diabetes. The Commentary advised that intermediate-acting basal insulin (human isophane insulin) is also PBS-listed. The PBAC noted that insulin glargine (Lantus) is the most commonly prescribed basal insulin for T2DM in Australia and that human isophane is rarely used now.

- Exenatide belongs to the same pharmacological class as lixisenatide.
 - Exenatide (twice daily) is the only GLP-1 receptor agonist currently listed on the PBS for use in combination with insulin.
 - The results of a survey of Australian endocrinologists commissioned by the sponsor suggested that basal insulin plus exenatide is the treatment most likely to be replaced by insulin glargine with lixisenatide FRC. Utilisation estimates presented in Section 4 of the submission suggested that basal insulin plus rapid insulin, premixed insulin, and basal insulin plus an SGLT2 inhibitor were the treatments most likely to be replaced.
- 5.2 The Commentary noted that insulin in combination with exenatide twice daily is an appropriate comparator. The submission noted that other anti-diabetic agents may be added to basal insulin in patients with inadequate control on basal insulin (plus metformin), including:
- oral agents (sulfonylureas, DPP4 inhibitors, SGLT2 inhibitors);
 - GLP-1 agonists;
 - Addition of rapid-acting insulin one to three times per day, or the use of premixed insulin.
- 5.3 These agents may also be appropriate comparators. 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).
- 5.4 Liraglutide (a GLP-1 agonist) is a potential near comparator. A submission for liraglutide for use in combination with insulin for patients with Type 2 diabetes and high cardiovascular risk was considered and rejected by the PBAC at the July 2017 meeting (Liraglutide PSD, July 2017).
- 5.5 Given that insulin glargine with lixisenatide FRC is formulated as a FRC, with differences in lixisenatide dosing and bioavailability compared to the individual agents, the individual components of insulin glargine and lixisenatide administered concomitantly is also a potential comparator, noting that lixisenatide is not PBS listed.
- 5.6 The Pre-Sub-Committee Response (PSCR) identified that thiazolidinediones and acarbose were unlikely to be substituted treatments due to them not being highly used in Australia. The ESC advised that it agreed that these drugs were not widely used in Australia for the control of Type 2 diabetes.

- 5.7 The ESC advised that insulin with exenatide twice daily was an appropriate comparator and noted that there are a number of other possibilities given the range of insulin regimes in practice. The ESC further advised that it was difficult to determine which regimes would be replaced or displaced by the proposed listing.
- 5.8 The PBAC considered that insulin with exenatide twice daily was the appropriate comparator and noted the alternative comparators of 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).

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 organisations (1) via the Consumer Comments facility on the PBS website. The comments from Diabetes Australia were supportive of the proposed listing.

Clinical trials

- 6.3 The submission was based on an indirect comparison of insulin glargine with lixisenatide FRC to insulin glargine plus exenatide twice daily using insulin glargine as common reference:
- Insulin glargine with lixisenatide FRC versus insulin glargine (LIXILAN-L);
 - Insulin glargine plus exenatide twice daily versus insulin glargine (GWCO).
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
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.
	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.	<i>Diabetes Care</i> 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.	<i>Diabetes Obes Metab</i> 2017; 19(10):1408-1415.
	Aroda VR, Rosenstock J, Wysham C et al. Efficacy and safety of LixiLan, a fixed-ratio combination of insulin glargine plus lixisenatide in Type 2 diabetes not adequately controlled on basal insulin: LixiLan-L trial [Conference abstract].	<i>Diabetologia</i> . 2016; 59 (Supp 1):S2-S3.
	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.	<i>Diabetologia</i> 2016; 59 (Supp 1): S382-S383
GWCO	Buse JB, Bergenstal RM, Glass LC et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes.	<i>Annals of Internal Medicine</i> 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.	<i>Diabetes Care</i> 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.	<i>Diabetologia</i> 2012; 55 (Suppl. 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].	<i>Diabetes</i> 2011; 60 (Suppl. 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.	<i>Diabetologia</i> 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.	<i>Current Medical Research and Opinion</i> 2014; 30 (7): 1209-1218.

Source: Table 2.2.1, pp37-38 of the submission.

6.5 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Insulin glargine with lixisenatide FRC versus insulin glargine					
LIXILAN-L	736	Randomised, active-controlled, open-label, parallel group, multi-centre trial (30-weeks with 6-week run-in phase).	<i>High</i>	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 (primary), HbA1c strata; 2-hour plasma glucose excursion, body weight, 7-point SMPG, FPG, insulin glargine dose, EQ-5D-3L VAS, IWQoL-Lite, TRIM-D.
Insulin glargine plus exenatide (twice daily) versus insulin glargine plus placebo					
GWCO	259	Randomised, placebo-controlled, double-blind, parallel group, multi-centre trial (30-weeks).	<i>Unclear</i>	Adults with Type 2 diabetes who have inadequate glycaemic control on insulin glargine (≥ 20 units/day) +/- metformin +/- pioglitazone.	Change from baseline in HbA1c (primary), HbA1c strata, body weight, 7-point SMPG, FPG, insulin glargine dose, lipid parameters, cardiovascular parameters.

Source: Table 2.2.2, p.39 of the submission.

Abbreviations: 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.

- 6.6 Baseline characteristics appeared well balanced between treatment arms in the LIXILAN-L trial. There were differences in some baseline characteristics between treatment arms in the GWCO trial, including a higher proportion of male subjects, higher baseline HbA1c, a higher proportion of patients on metformin only, and a lower proportion on metformin and pioglitazone in the insulin glargine plus placebo group.
- 6.7 Mean patient age and duration of diabetes were broadly similar between the LIXILAN-L and GWCO trials. There were major differences between the trials in gender, ethnicity, BMI, baseline HbA1c, FPG level and HDL cholesterol. Mean insulin requirements at baseline were notably higher in the GWCO trial compared to LIXILAN-L trial (48 units in GWCO compared to 35 units in the LIXILAN-L trial).
- 6.8 Patients screened for the LIXILAN-L trial completed a 6-week run-in phase during which background oral hypoglycaemic medications apart from metformin were ceased, and patients receiving basal insulins other than insulin glargine were switched to insulin glargine. At the end of the run-in phase, the mean HbA1c decreased from 8.53% (screening visit) to 8.08% (baseline). There was no run-in period for the GWCO trial. The ESC advised that the use of a run-in period further confounded the comparability of the baseline characteristics between the LIXILAN-L and GWCO trials.
- 6.9 In the LIXILAN-L trial, dose changes were made based on the median of fasting glucose values for the prior 3 days. The same titration schedule was used for both the insulin glargine with lixisenatide FRC and the insulin glargine groups, and was based on adjustment of the insulin glargine dose. In the GWCO trial, participants recorded self-monitored blood glucose, and adjustments to insulin dose were

made by the investigator at least weekly from week 5 to week 10, and every 2 weeks thereafter. The titration algorithm used in the GWCO trial allowed for more aggressive titration of insulin dose compared to the LIXILAN-L trial.

- 6.10 In the GWCO trial, exenatide was initiated at a dose of 5 mcg twice daily and increased to the final dose of 10 mcg twice daily after 4 weeks. In the LIXILAN-L trial, the lixisenatide dose was adjusted concurrently according to the insulin dose, and was also influenced by the strength of FRC pen used. The maximum daily dose was 60 units/20 mcg for insulin glargine with lixisenatide FRC and 60 units for insulin glargine. If a higher dose was required to maintain glucose parameters below the threshold values, a rescue therapy was introduced (insulin glulisine). There was no reported maximum insulin dose in the GWCO trial.
- 6.11 There were significant differences in treatment characteristics between the trials in terms of study design (six-week run-in period in the LIXILAN-L trial vs no run-in for the GWCO trial), permitted concomitant medications (metformin vs metformin +/- pioglitazone), titration schedules, and treatment targets (≤ 7.8 mmol/L vs < 5.6 mmol/L) which suggest that the trials may not be sufficiently exchangeable for indirect comparison.
- 6.12 The ESC noted that other trials referenced in the TGA Product Information may also be informative in assessment of the effectiveness of the product, including the getgoal X study.
- 6.13 The PBAC noted the above trials provided and the differences between trials.

Comparative effectiveness

- 6.14 Table 4 summarises the results of HbA1c outcomes for the LIXILAN-L trial.

Table 4: Key results for the LIXILAN-L trial

	Insulin glargine with lixisenatide FRC	Insulin glargine	Treatment difference (95% CI)
HbA1c at Week 30, % (primary outcome)			
Baseline, mean (SD)	8.07 (0.68)	8.08 (0.73)	
Change from baseline, LS mean (SD)	-1.13 (0.06) N=364	-0.62 (0.06) N=364	-0.52 (-0.63, -0.40)
HbA1c responders at Week 30, n (%)			
HbA1c <7%	201 (54.9) N=366	108 (29.6) N=365	25.5 (18.9, 32.1)

Source: Table 2.5.1, p.72 and Table 2.5.2, p.73 of the submission.

Abbreviations: FRC, fixed ratio combination; CI, confidence interval; HbA1c, glycosylated haemoglobin; SD, standard deviation.

- 6.15 Treatment with insulin glargine with lixisenatide FRC was associated with a statistically significant reduction in HbA1c at Week 30 (-0.52%; 95% CI -0.63, -0.40), and a statistically significantly higher proportion of patients achieving HbA1c <7% compared to insulin glargine (25.25%; 95% CI 18.94, 32.10).

- 6.16 Treatment with insulin glargine with lixisenatide FRC was also associated with statistically significant improvements in 2-hour plasma glucose excursion, mean body weight, 7-point self-monitored plasma glucose profiles, proportion of patients requiring rescue therapy, and EQ-5D-3L visual analogue scale (VAS) scores compared to treatment with insulin glargine. There were no statistically significant differences between treatment arms for the change in insulin dose at 30 weeks. Treatment with the insulin glargine with lixisenatide FRC did not appear to be associated with an insulin-sparing effect. The PBAC considered that the insulin-sparing effect claimed in the submission was not supported and that the differences in insulin glargine dose at week 30 likely reflected the differences in baseline insulin requirements for patients recruited in the two trials, possibly due to the differences in BMI across the trials.
- 6.17 Approximately 27% of patients were reported to be on the maximum permitted insulin glargine with lixisenatide FRC dose of 60 units/20 mcg at Week 30, suggesting a ceiling effect on treatment titration, which may have affected the trial efficacy and safety outcomes. At Week 30, the mean daily dose of lixisenatide was 16.9 mcg, with 29.6% of patients receiving doses of 10 mcg to 15 mcg, and 68.8% of patients receiving doses of 15 mcg to 20 mcg. Patients on lower lixisenatide doses may not achieve the full benefit of GLP-1 agonist treatment. The PBAC noted that the capping of dose may have limited the final mean insulin dose in the LIXILAN-L trial.
- 6.18 Table 5 presents the results of the indirect comparison for insulin glargine with lixisenatide FRC and insulin glargine plus exenatide for the primary outcome of change from baseline in HbA1c 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)
Change from baseline in HbA1c at 30 weeks LSM (SE)				
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)
Indirect WMD, 95% CI (result <0 favours FRC)				0.17 (-0.09, 0.43)

Source: Table 2.6.4, p.99 of the submission.

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

- 6.19 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). The upper 95% confidence limit exceeded the nominated non-inferiority margin of 0.3% to 0.4%, and therefore non-inferiority was not demonstrated.

- 6.20 There was no statistically significant difference between insulin glargine with lixisenatide FRC and insulin glargine plus exenatide for patients reaching HbA1c targets of <7% or ≤6.5%. Differences between the LIXILAN-L and GWCO trials in baseline HbA1c, titration algorithms and treatment targets suggest that the results for these outcomes should be interpreted with caution.
- 6.21 Both insulin glargine with lixisenatide FRC and insulin glargine plus exenatide were associated with statistically significant reductions in body weight at Week 30 compared to insulin glargine. However, weight reductions for insulin glargine plus exenatide (-2.74 kg; 95% CI: -3.74, -1.74) were numerically greater than for insulin glargine with lixisenatide FRC (-1.37 kg; 95% CI: -1.81, -0.93). Differences in baseline BMIs between the studies suggest that this result should be interpreted with caution.
- 6.22 Treatment with insulin glargine plus exenatide was associated with a statistically significant reduction in insulin glargine dose compared to the insulin glargine arm (-6.5 units/day; 95% CI: -12.3, -0.8), whereas there was no statistically significant difference in insulin dose for insulin glargine with lixisenatide FRC compared to insulin glargine (-0.3 units/day; 95% CI: -1.8, 1.3). The PBAC noted that there was no statistically significant difference in insulin dose for insulin glargine with lixisenatide compared with insulin glargine alone in LIXILAN-L.
- 6.23 The submission presented a matching adjusted indirect comparison (MAIC) for change in HbA1c from baseline, and for the proportion of subjects reaching HbA1c targets (<7% and ≤6.5%), based on individual patient data from the LIXILAN-L trial and aggregate data from the GWCO trial.
- 6.24 Three matching scenarios were included in the submission:
- Scenario 1 matched for variables with an impact on outcomes (potential confounders) with different distributions between the trials, including gender, ethnicity, baseline weight, baseline HbA1c, baseline systolic blood pressure, baseline HDL cholesterol, concomitant medication, and insulin dose units/kg. Matching for these variables resulted in almost 100% loss of patients from the sample due to poor overlap between the trial populations, and could not be used to generate meaningful results.
 - Scenario 2 matched for variables interacting with the study treatment (treatment effect modifiers) with different distributions across the trials, including concomitant medication, baseline weight, baseline triglycerides, baseline FPG level. Matching for these variables resulted in a 68% loss of patients from the sample.
 - Scenario 3 matched for variables that interacted with the study treatment and had an impact on outcomes with different distributions between the trials,

including concomitant medication, baseline weight, and baseline triglycerides. Matching for these variables resulted in a 64% loss of patients from the sample.

6.25 The LIXILAN-L results before and after matching for Scenarios 2 and 3, along with the results of the MAIC versus the GWCO trial are presented in Table 6.

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

	Insulin glargine with lixisenatide FRC	Insulin glargine	Insulin glargine plus exenatide	Mean difference (95% CI)
Change in HbA1c at 30 weeks				
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)
Indirect estimate Scenario 2 (Result <0 favours FRC)				0.09 (-0.18, 0.36)
Indirect estimate Scenario 3 (Result <0 favours FRC)				0.09 (-0.18, 0.36)

Source: Table 2.6.9, p.103 of the submission; 'Soliqua – additional data for MAIC analysis' Excel workbook.

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

6.26 Matching in Scenarios 2 and 3 had minimal effect on the insulin glargine with lixisenatide FRC treatment arms, but reduced the HbA1c changes in the common reference arm. The differences between the insulin glargine treatment arm point estimates for the LIXILAN-L and GWCO trials increased post-matching suggesting that the matching performed may have reduced the exchangeability of the trials.

6.27 For the outcome of change in HbA1 at Week 30, the matching undertaken in Scenarios 2 and 3 resulted in an upper 95% confidence interval of 0.36. The submission claimed 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.

6.28 The Commentary reported that the results of the MAICs were not considered to be robust due to the following reasons:

- The analyses were conducted post hoc and were considered to be at high risk of bias.
- There was insufficient overlap between the LIXILAN-L and GWCO trials to allow matching of baseline patient characteristics that were potential confounders (such as baseline insulin dose, and baseline HbA1c).
- The submission presented alternative scenarios (Scenario 2 and 3) which matched for treatment effect modifiers but did not address identified differences in baseline characteristics that had an impact on treatment outcomes. The large weightings applied across a few individuals in Scenarios 2 and 3 may have affected other (potentially confounding) patient characteristics that were not matched in these scenarios. However, post-matching baseline characteristics for

the non-matched variables (potential confounders) were not provided, and therefore the impact of the matching on these variables could not be assessed. The differences between the insulin glargine treatment arm point estimates for the LIXILAN-L and GWCO trials suggest that the matching performed may have reduced the exchangeability of the trials.

- Underlying differences in trial design (lead-in periods, titration protocols, treatment targets) were not addressed by the MAIC.
- 6.29 The ESC noted the MAIC analyses try to account for some of the differences across the studies and the sponsor’s acknowledgment in the PSCR of the difficulties associated with the indirect treatment comparison (ITC) undertaken.
- 6.30 The ESC noted the PSCR statement that “iGlarLixi simplifies the management of T2DM management, and in practice, this is expected to result in increased adherence, leading to better glycaemic control in the real world setting. Results of any ITC conducted using clinical trial data, captured in a highly controlled environment, are unlikely to capture this.”
- 6.31 The ESC noted the small numbers involved in the adjusted data from the LIXILAN-L study as well as the differences in the trial design and trial populations noted above including the use of the run in period for LIXILAN-L, differences in BMI, HbA1c at baseline and in the adjustment of insulin dosing across the studies. The ESC noted 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.
- 6.32 The PSCR stated that the insulin dose was capped in the control arm of the LIXILAN-L trial to allow meaningful comparisons to the product which provides a maximum insulin dose of 60 units and that the final insulin dose observed in the control arm of LIXILAN-L was 47 units despite the 60 unit cap. The PSCR presented a simulation to attempt to demonstrate that dose capping did not have a material impact on glycaemic efficacy.
- 6.33 The Pre-PBAC Response (p2) further added that similar fasting plasma glucose levels were achieved in each treatment arm of the LIXILAN-L trial, indicating successful titration to the target, which is primarily mediated by insulin glargine and that treatment with iGlarLixi resulted in a significantly greater HbA1c change from baseline to insulin glargine alone.

Comparative harms

- 6.34 Table 7 presents a summary of the treatment-emergent adverse events reported in the LIXILAN-L trial.

Table 7: Summary of treatment-emergent adverse events for the LIXILAN-L trial [n (%)]

	Insulin glargine with lixisenatide FRC N=365	Insulin glargine N=365
Serious AE	20 (5.5)	18 (4.9)
Treatment related AE	52 (14.2)	3 (0.8)
Discontinuation due to AE	10 (2.7)	3 (0.8)
AE leading to death	1 (0.3)	2 (0.5)
Any AE	195 (53.4)	191 (52.3)
- Nausea	38 (10.4)	2 (0.5)
- Nasopharyngitis	32 (8.8)	32 (8.8)
- Headache	21 (5.8)	10 (2.7)
- Diarrhoea	16 (4.4)	10 (2.7)
- Vomiting	13 (3.6)	2 (0.5)
Documented symptomatic hypoglycaemia	146 (40.0)	155 (42.5)

Source: Table 2.5.14, p.84 of the submission; Table 16.2.7.1.8, p.163 of Appendix 16.2.7 of the insulin glargine with lixisenatide FRC clinical study report.

Abbreviations: AE, adverse event; FRC, fixed ratio combination.

- 6.35 There were numerically higher treatment-related adverse events, and discontinuations due to adverse events in the insulin glargine with lixisenatide FRC group. The most frequently reported treatment-related adverse events were nausea (8.8%), vomiting (2.5), diarrhoea (2.5%), and dizziness (1.4%). Rates of serious adverse events were similar between arms. Three patients experienced adverse events leading to death, including one in the FRC group (pneumonia) and two in the insulin glargine group (gallbladder cancer and cardiopulmonary failure).
- 6.36 The submission provided indirect comparisons between insulin glargine with lixisenatide FRC and insulin glargine plus exenatide for treatment-emergent adverse events, serious adverse events, discontinuations due to adverse events, and adverse events leading to death.
- 6.37 The submission noted that the most common treatment emergent adverse event leading to treatment discontinuation was nausea, and argued that lower rates of nausea with insulin glargine with lixisenatide FRC compared to insulin glargine with exenatide would be expected to result in better treatment adherence in the real world setting. There may be potential for lower rates of nausea with the insulin glargine with lixisenatide FRC due to use of potentially submaximal doses of lixisenatide when dosed as part of the FRC. However, the results of the indirect comparison of safety outcomes should be interpreted with caution due to the differences between the trials in terms of baseline characteristics and trial design. The open-label design of the LIXILAN-L trial may have influenced the reporting and management of adverse events.
- 6.38 The ESC noted that comparative toxicity appeared to be similar and 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 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.

- 6.39 The Pre-PBAC Response (p1-2) acknowledged the difficulties comparing insulin glargine with lixisenatide FRC with the comparator, and claimed that it was reasonable to assume that the lower withdrawal rate observed in LIXILAN-L was reflective of the gradual increase in lixisenatide dose offered by iGlarLixi, leading to fewer gastrointestinal events than typically observed for GLP-1 receptor agonists.

Interpretation of clinical evidence

- 6.40 The submission described insulin glargine with lixisenatide FRC as non-inferior in terms of effectiveness and safety compared with concomitant insulin glargine plus exenatide twice daily.
- 6.41 The Commentary considered that the clinical claim presented in the submission was not adequately supported.
- Significant differences between trials in terms of study design, baseline characteristics, permitted concomitant medications, titration schedules, and treatment targets, suggested that the trials were unsuitable for indirect comparison.
 - The results of a conventional indirect comparison for change in HbA1c from baseline failed to meet the nominated non-inferiority margin of 0.3-0.4 for change in HbA1c from baseline.
 - There was insufficient overlap between the LIXILAN-L and GWCO trials to allow matching of baseline patient characteristics that were potential confounders (such as baseline insulin dose, and baseline HbA1c).
 - Alternative MAIC scenarios which corrected for differences in treatment effect modifiers resulted in an upper confidence interval of 0.36 which was within the nominated non-inferiority of 0.4. However, the large weightings applied across a few individuals may have affected other patient characteristics that were not matched in these scenarios. Post-matching baseline characteristics for the non-matched variables (potential confounders) were not provided, and therefore the impact of the matching on these variables could not be assessed. The differences between the insulin glargine treatment arm point estimates for the LIXILAN-L and GWCO trials increased post-matching suggesting that the matching performed may have reduced the exchangeability of the trials.
- 6.42 The ESC advised that the clinical claim presented in the submission was not adequately supported by the evidence provided with the submission. The PSCR agreed with the Commentary, that the differences in the trial populations made an

indirect comparison difficult and that due to this, results of the unadjusted ITC should be interpreted with caution. The sponsor stated that the MAIC was conducted in an attempt to control for the differences across trials, however the reduction in sample size introduce a level of uncertainty, but argued that modifiers and treatment confounders were adjusted for and the MAIC and the meta-regression presented in the submission, which contained the full sample size, supported the claim of non-inferiority. The Pre-PBAC Response reiterated the above statements from the PSCR.

- 6.43 Overall the PBAC considered the claim of non-inferior comparative effectiveness to be uncertain, but may be reasonable given the key parameters which varied across the trials appear to not be treatment effect modifiers and non-inferiority was demonstrated with a 0.4% margin using the MAIC analysis.
- 6.44 On balance, the PBAC considered that insulin glargine with lixisenatide FRC was non-inferior in comparative safety to the comparator. The PBAC agreed that the claim of reduced gastrointestinal adverse events was not adequately supported due to the reduced dose of lixisenatide compared with exenatide in the trials and the open-label design.

Economic analysis

- 6.45 The submission presented a cost minimisation analysis comparing insulin glargine with lixisenatide FRC to insulin glargine plus exenatide (twice daily).
- 6.46 The proposed equi-effective doses were based on the average daily doses at Week 30 of the LIXILAN-L and GWCO trials:
- 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.
- 6.47 The following issues relating to the proposed equi-effective were noted:
- The equi-effective doses assume that treatment with insulin glargine with lixisenatide FRC is associated with a lower insulin glargine requirement compared to treatment with insulin glargine plus exenatide. However, the differences in insulin glargine dose at Week 30 likely reflect the differences in baseline insulin requirements for patients recruited for the LIXILAN-L and GWCO trials. The PBAC agreed that there was no evidence of an insulin-sparing effect and that the differing insulin levels used were likely reflective of the different baseline insulin requirements for patients recruited for the LIXILAN-L and GWCO trials.
 - The doses of insulin glargine with lixisenatide FRC and insulin glargine in the LIXILAN-L trial were capped at 60 units/20 mcg and 60 units respectively, which may have limited the average dose achieved at Week 30 in the LIXILAN-L trial,

while no cap was applied in the GWCO trial. The PBAC agreed that the capping of dose was a confounding factor in determining the equi-effective dose.

- Treatment with insulin glargine plus exenatide was associated with a statistically significant reduction in insulin glargine dose compared to the insulin glargine arm (-6.5 units/day; 95% CI: -12.3, -0.8) in the GWCO trial. In the LIXILAN-L trial there was no statistically significant difference in insulin dose for insulin glargine with lixisenatide FRC compared to insulin glargine (-0.3 units/day; 95% CI: -1.8, 1.3). Therefore, the implied insulin-sparing effect for the insulin glargine with lixisenatide FRC over insulin glargine plus exenatide does not appear to be supported by the results of the LIXILAN-L trial as insulin glargine with lixisenatide FRC did not demonstrate a reduction in insulin glargine use compared to the control arm. The PBAC agreed that no reduction in insulin glargine dose was demonstrated by the data.
 - The proposed dose relativity was not consistent with previous evidence considered by the PBAC (lixisenatide for dual therapy with metformin or triple therapy with metformin and a sulfonylurea) which suggested that lixisenatide may be inferior to exenatide on a mcg to mcg basis (Paragraph 7.5; July 2014 lixisenatide PSD). The Pre-Sub-Committee Response (PSCR) argued that this was because these calculations were not for combination use with insulin as they have complementary modes of action. The PBAC considered that this complicated determining the appropriate equi-effective dose but did not justify a difference in the relative doses for lixisenatide and exenatide
- 6.48 The submission derived the cost per unit of insulin glargine, and the cost per mcg of exenatide 5 mcg and 10 mcg based on the reference price (price at first listing). The submission claimed to have used the effective prices for insulin glargine and exenatide 5 mcg and 10 mcg at the time of first listing, however, these prices could not be verified during the evaluation. Whilst this is not the usual approach to pricing medicines, the 2017 Strategic Agreement between Government and Medicines Australia does allow a higher price to be awarded to some cost-minimised medicines in limited circumstances (Clause 5.7 of the agreement). This is a policy matter and not a PBAC matter. The ESC noted this was not a matter for the PBAC to advise on. In line with usual practice, PBAC should provide advice on the equi-effective doses of medicines recommended for listing on a cost-minimisation basis.
- 6.49 The cost of treatment per day was calculated using the mean daily doses of insulin glargine plus exenatide at Week 30 in the GWCO trial (62.5 units/day insulin glargine and 19.3 mcg/day exenatide). The daily cost of exenatide was weighted between the 5 mcg (7%) and 10 mcg strengths (93%), based on the weighting required to achieve a dose of 19.3 mcg.
- 6.50 A cost offset for reduction of needle use (50% of reduction in cost for 2 needles) was included. The needle cost offset was based on a cost of \$0.32 per needle,

which may be higher than the applicable National Diabetes Services Scheme (NDSS) price.

- 6.51 The submission calculated the FRC lixisenatide component cost by deducting the cost of the FRC insulin component from the total daily cost of insulin glargine plus exenatide. The submission assumed that the price per unit for insulin in combination is the same as the individual agent and therefore any differences in price between the FRC and comparators was attributed to the lixisenatide component. This resulted in a substantially higher price per microgram for lixisenatide compared to exenatide which does not appear to be justifiable based on the current available evidence. The PBAC agreed that this higher cost per microgram was not justified.
- 6.52 The ESC noted that the equi-effective doses were developed based on the unadjusted population in which the non-inferiority margins were not achieved. The ESC advised that it may have been more appropriate to base the equi-effective doses on the MAIC results given that the submission's claim of non-inferiority was based on the results of the MAIC. The ESC noted that the PSCR stated that there was no significant change in mean insulin dose following adjustment in the MAIC. The Pre-PBAC Response again reiterated the claim made in the PSCR. The PBAC considered differences across the trials in terms of design and patient characteristics is likely to have impacted on the doses used.
- 6.53 The ESC noted that the equi-effective doses proposed were different to those provided in previous submissions and assumed that treatment with insulin glargine with lixisenatide FRC was associated with a lower insulin glargine requirement when compared to use with exenatide. The PSCR argued that this was because the dose may be different when used in combination with insulin. The ESC advised that the data did not support this statement as the comparison was uncertain given the variation in the baseline characteristics in the trial populations and the methodology differences. The ESC advised that calculating an equi-effective dose was difficult and the claim of an insulin sparing effect was uncertain given the differences across the trials. The PBAC considered that the proposed dose relativity was not supported by the evidence provided.
- 6.54 The ESC considered the economic analysis uncertain given the product cost is significantly higher than for insulin glargine per dose, and given the potential for use outside the restriction and the potential for the product to replace less costly PBS listed medicines. The PBAC agreed that this was not justified and was not acceptable based on the evidence provided.

Drug cost/patient/year: \$ [REDACTED] (3 units/1 mcg pen)

- 6.55 3 units/1 mcg pen: At the requested DPMQ of [REDACTED] for [REDACTED] pens (300 units/100 mcg insulin glargine/lixisenatide per pen), assuming [REDACTED] scripts per year (based on 51.47 units/17.16 mcg per day), the price per patient per year is \$ [REDACTED]
- 6.56 2 units/1 mcg pen: At the requested DPMQ of \$ [REDACTED] for [REDACTED] pens (300 units/150 mcg insulin glargine/lixisenatide per pen), assuming [REDACTED] scripts per year (based on 30.42 units/15.21 mcg per day), the price per patient per year is \$ [REDACTED]
- 6.57 The DPMQ was recalculated using the effective price to be \$ [REDACTED] for [REDACTED] pens for the 3 units/1 mcg pen and \$ [REDACTED] for the 2 units/1 mcg pen.
- 6.58 Based on the effective prices, the price per patient per year is \$ [REDACTED] for the 3 units/1 mcg pen and \$ [REDACTED] for the 2 units/1 mcg pen.
- 6.59 The PBAC was of the view that this represented a significant increase in price compared with the comparator. It considered that the basis for this, that less insulin was used in LIXILAN-L compared to GWCO to achieve similar HbA1c reductions, was not supported by the data.

Estimated PBS usage & financial implications

- 6.60 This submission was considered by DUSC.
- 6.61 The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of insulin glargine with lixisenatide FRC.
- 6.62 The submission identified the following PBS reimbursed insulin treatment regimens that were likely to be substituted by insulin glargine with lixisenatide FRC:
- insulin glargine plus exenatide;
 - insulin glargine plus DPP4 inhibitor (sitagliptin or linagliptin);
 - insulin glargine plus SGLT2 inhibitor (dapagliflozin or empagliflozin);
 - insulin glargine plus rapid insulin (insulin aspart, glulisine, lispro, insulin human neutral, insulin neutral bovine);
 - premixed insulin (isophane human/neutral human, lispro/lispro protamine).
- 6.63 The submission excluded sulfonylureas, thiazolidinediones and acarbose from the analysis. This may not be reasonable, as the addition of a sulfonylurea, thiazolidinedione, or acarbose may also be considered for patients inadequately controlled on basal insulin (+/- metformin).

6.64 Table 8 presents the estimated utilisation and financial impact of insulin glargine with lixisenatide FRC over the first six years of listing.

Table 8: Total utilisation and cost to the PBS of listing insulin glargine with lixisenatide FRC

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 2022	Year 6 2023
Estimated eligible population						
Basal insulin + exenatide						
Basal insulin + DPP4						
Basal insulin + SGLT2						
Basal + rapid insulin						
Premixed insulin						
Total						
Estimated insulin glargine with lixisenatide FRC uptake						
Basal insulin + exenatide	%	%	%	%	%	%
Basal insulin + DPP4	%	%	%	%	%	%
Basal insulin + SGLT2	%	%	%	%	%	%
Basal + rapid insulin	%	%	%	%	%	%
Premixed insulin	%	%	%	%	%	%
Estimated displaced scripts						
Basal insulin + exenatide						
Basal insulin + DPP4						
Basal insulin + SGLT2						
Basal + rapid insulin						
Premixed insulin						
Total FRC patients						
Total cost of listing insulin glargine with lixisenatide FRC (2 units/1 mcg: 27.5%; 3 units/1 mcg: 72.5%)						
Total FRC patients						
Total FRC scripts						
Additional metformin scripts						
Cost to PBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Displaced scripts						
Cost to PBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Net changes to the PBS/RPBS						
Net cost to PBS	\$	\$	\$	\$	\$	\$
Net co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS (less co-payments)	\$	\$	\$	\$	\$	\$

Source: Table 8 of commentary which used submission Table 4.3.2, p.127; Table 4.3.4, pp129-130; Table 4.3.5, p.130; Table 4.3.6, p.131; Table 4.3.7, p.132; Table 4.3.10, pp134-135; Table 4.4.6, p.137; Table 4.5.1, pp138-139; Table 4.6.4, p.140 of the submission. Abbreviations: DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter 2; FRC, fixed ratio combination.

6.65 The submission estimated a net cost to the PBS in Year 6 to be less than \$10 million. The estimated cumulative net cost over six years was \$30 - \$60 million.

- 6.66 The PBAC noted advice from the Department that the co-payments for the drugs offset in the financial estimates were higher than for insulin glargine with lixisenatide FRC therefore the net cost to the PBS less co-payments, from listing, was higher than without the co-payment.
- 6.67 The PBAC considered that the utilisation/financial estimates were uncertain because:
- The estimates did not account for patients treated with PBS-listed intermediate-acting basal insulin (insulin isophane).
 - 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 government. The DUSC also considered this to be a risk. The Pre-PBAC Response (p3) claimed that the restriction was designed to ensure that only the proposed patients were eligible to access insulin glargine with lixisenatide FRC and that it was unlikely that insulin naïve patients would move to insulin glargine with lixisenatide FRC without first initiating basal insulin.
 - The submission excluded other, potentially less costly oral treatments which may also be substituted (basal insulin plus sulfonylureas). The DUSC noted that the cost offsets may have been over-estimated due to exclusion of some of the cheaper medicines. The Pre-PBAC Response (p3) claimed that as the proposed PBS restriction is for patients with inadequate glycaemic control on basal insulin, substitution was considered to come from current intensification options which excluded sulfonylureas, thiazolidinediones and acarbose. The Pre-PBAC response also claimed that the financial estimates were conservative due to exclusion of cost offsets related to the reduced use of consumables.
 - The PBAC and the DUSC considered that there is significant risk of wastage not accounted for in the submission. The Pre-PBAC Response (p3) claimed that due to the reduced gastrointestinal side effects of insulin glargine with lixisenatide FRC, the wastage outlined by the DUSC was unlikely to occur. The Pre-PBAC response also noted that the number of pens requested to be supplied per script was consistent with other insulin products, and that it would be willing to negotiate the maximum quantity if required.
 - Assessment of insulin utilisation is difficult due to the large quantity of insulin supplied per dispensing, and the large inter-patient variation in insulin dose. The long treatment coverage periods assumed in the financial impacts may not adequately discriminate between concomitant treatment, treatment switching, and discontinuations.

- The role of basal insulin up-titration to achieve glycaemic control was not explored in the financial impacts, but is likely to represent an alternative treatment option for some patients.
- The assumed average insulin doses used in the financial impacts were based on clinical trial utilisation and may not reflect the average doses used in the Australian population.
- In the LIXILAN-L trial, a number of patients reached the upper limit of dosing for the insulin glargine with lixisenatide FRC (60 units/20 mcg). The financial impacts did not account for potential attrition of patients with increasing insulin requirements over time.
- There is potential for higher than forecast uptake due to the convenience of the insulin glargine with lixisenatide FRC treatment regimen (a once daily subcutaneous injection), and the reduction in patient co-payments associated with insulin glargine with lixisenatide FRC compared to other treatments. The DUSC considered that the uptake rates assumed in the submission were uncertain and that those proposed were lower than were indicated in the survey of endocrinologists. The Pre-PBAC Response (p3) noted that the uptake rate was based on segment 3, i.e. patients uncontrolled on basal insulin with or without oral agents, of the endocrinologist survey, assuming substitution rates indicated by endocrinologists in year 1 of the model.

Quality Use of Medicines

- 6.68 The submission identified the 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 as the main quality use of medicines issues.
- 6.69 The following quality use of medicines issues were identified during the evaluation:
- Patients are required to cease all oral antidiabetic therapies apart from metformin when switching to the insulin glargine with lixisenatide FRC, and patients generally initiate insulin glargine at a dose lower than current insulin use. This may result in a loss of glycaemic control during the transition. Additional medical supervision is likely to be required during the transition period.
 - There is loss of treatment flexibility associated with the FRC, as the components cannot be titrated individually, and the lixisenatide dose is dependent on the basal insulin requirements. Patients treated with the FRC may receive lower than the TGA recommended dose of lixisenatide when used as an individual agent (Lyxumia) in combination with metformin, metformin and sulphonylurea, basal insulin and metformin, basal insulin and sulphonylurea. Given the absence of

evidence that a lower dose is sufficient when used as an FRC in combination therapy, patients may not obtain the full benefit of GLP-1 agonist therapy.

- There is 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.
 - Patients who reach the maximum dose of insulin glargine with lixisenatide (60 units/20 mcg) are required to switch to an alternative treatment, which may result in loss of glycaemic control during the transition.
- 6.70 The PSCR argued that the lack of flexibility in the FRC is inherent to the design of the product and increases simplicity of treatment, noting that the gradual increase in lixisenatide dose offered by the product results in fewer gastrointestinal side effects than typically observed with GLP-1 receptor agonists. The PSCR added that although lixisenatide must be increased or decreased alongside insulin glargine, the range of dosing options provided by the two pens is greater than that of the individual agents, or of exenatide. The Pre-PBAC Response reiterated the arguments made in the PSCR.
- 6.71 The DUSC considered that there was a risk of intentional or inadvertent quadruple therapy, through addition rather than substitution by FRC.
- 6.72 The DUSC considered that there were significant dosage issues related to the fixed ratio combination, including the question of whether the lixisenatide dose would be adequate and challenges for patients needing higher doses of insulin glargine.
- 6.73 The Pre-PBAC Response outlined the sponsor's risk management plan including guidance for healthcare providers, and noted for patients requiring more than 60IU insulin glargine, insulin glargine with lixisenatide FRC should not be used.
- 6.74 The PBAC noted the quality use of medicines issued identified, noting the need for appropriate activities to be put in place.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend insulin glargine with lixisenatide fixed ratio combination (FRC) for the treatment of patients with Type 2 diabetes mellitus (T2DM) who have inadequate glycaemic control with basal insulin on the basis that the equi-effective doses proposed in the submission were not accepted and hence there was no basis for determining the cost-effective price for insulin glargine with lixisenatide FRC.
- 7.2 The PBAC noted that if listed, insulin glargine with lixisenatide FRC would be the first listing of lixisenatide on the PBS and the first FRC containing a glucagon-like peptide-1 agonist with basal insulin for T2DM.

- 7.3 The PBAC agreed with the proposed clinical place for the product; however it considered that there was a likelihood of use outside of the proposed restriction to patients using other oral agents or basal insulin as the restriction is narrower than the TGA indication. In addition there is the potential for use as quadruple therapy and use of doses higher than 60 units insulin glargine equivalents per day.
- 7.4 The PBAC agreed that the proposed comparator, insulin glargine once daily and exenatide twice daily, was appropriate and noted alternative comparators (see paragraph 5.8), which may be displaced if insulin glargine with lixisenatide FRC was listed due to convenience and patient preference for fewer injections.
- 7.5 The PBAC noted that the submission presented an indirect comparison of two clinical trials (LIXILAN-L and GWCO). The PBAC noted differences across the trials with respect to when they were conducted, design (including that the LIXILAN-L trial had a run-in phase whereas the GWCO trial did not) and patient characteristics (including gender, ethnicity and insulin dose). The PBAC noted that baseline HbA1c, duration of diabetes and BMI did not appear to be treatment effect modifiers and therefore it may be reasonable to conclude that the two trials were exchangeable, however considered this conclusion uncertain because of the general limitations of subgroup analyses and other factors not tested for may be treatment effect modifiers.
- 7.6 The PBAC noted that 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.
- 7.7 The PBAC noted the limitations of the MAIC as outlined in paragraph 6.28. 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.
- 7.8 Overall the PBAC considered the claim of non-inferior comparative effectiveness to be uncertain, but may be reasonable given the key parameters which varied across the trials appear to not be treatment effect modifiers and non-inferiority was demonstrated with a 0.4% margin using the MAIC analysis.
- 7.9 The PBAC advised that the claim of an insulin sparing effect was not supported given that there was no reduction in insulin glargine use compared to the control arm in the LIXILAN-L trial while this was demonstrated in the comparator trial. The

PBAC noted that the difference in the insulin doses used possibly reflected the different baseline insulin requirements for patients recruited in the LIXILAN-L versus GWCO trial.

- 7.10 The PBAC considered that the claim of non-inferior comparative safety was reasonable. The PBAC advised that the claim of reduced gastrointestinal adverse events was not adequately supported due to the reduced dose of lixisenatide compared with exenatide in the trials, however, on balance, the PBAC considered insulin glargine with lixisenatide FRC to be non-inferior to the comparator.
- 7.11 The PBAC noted the following equi-effective doses were proposed in the submission based on the average daily doses at week 30 in the LIXILAN-L and GWCO trials:
- 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.
- 7.12 The PBAC did not accept the claimed insulin sparing effect and thus did not accept a difference in the insulin glargine dose. The PBAC noted that the capping of the insulin glargine dose in the LIXILAN-L trial was also a potential confounding factor.
- 7.13 The PBAC noted the proposed dose relativity for lixisenatide and exenatide was not consistent with previous evidence considered by the PBAC (lixisenatide for dual therapy with metformin or triple therapy with metformin and a sulfonylurea) which suggested that lixisenatide may be inferior to exenatide on a mcg to mcg basis. The PBAC noted the sponsor's argument that it is not appropriate to extrapolate these findings to insulin glargine with lixisenatide FRC given the complementary modes of action of lixisenatide and insulin (PSCR). The PBAC considered that this did not justify a difference in the relative doses for lixisenatide and exenatide. The PBAC noted ESC's advice that it may have been more appropriate to base the equi-effective doses on the MAIC results given that the submission's claim of non-inferiority was based on the results of the MAIC. The PBAC considered differences across the trials in terms of design and patient characteristics is likely to have impacted on the doses used.
- 7.14 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 for insulin glargine with lixisenatide FRC.
- 7.15 The PBAC noted that while the eligible population figures were acceptable for the proposed population, the utilisation was likely underestimated due to probable use outside of the restriction, preferences for fewer injections and lower out of pocket

costs for consumers. In addition it was noted that there was the potential for the product to replace less costly PBS listed medicines.

- 7.16 The PBAC considered that any future resubmissions would need to be a major submission and address the uncertainties associated with the claim of non-inferior comparative effectiveness and provide further evidence to support equi-effective doses. Given the potential for use beyond the population proposed, the PBAC considered that a Risk Sharing Arrangement with an expenditure cap would be required.
- 7.17 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

The sponsor had no comment.