# 5.8 LIXISENATIDE,

# 10 micrograms/0.2 ml injection, 14 unit doses (&)

# 20 micrograms/0.2 ml injection, 14 unit doses,

# Lyxumia® Treatment Initiation Pack, 20 micrograms/0.2 ml injection, 2 x 14 unit doses,

# Lyxumia®, Sanofi-Aventis Australia Pty Ltd

**1 Purpose of Application**

* 1. The major submission sought an Authority required (STREAMLINED) listing for the treatment of type 2 diabetes in combination with insulin.
	2. It was also noted that an Authority required (STREAMLINED) listing for lixisenatide was concurrently sought for use as dual therapy in combination with metformin, and, as triple therapy in combination with metformin and a sulphonylurea, in type 2 diabetes (Agenda Item 5.9).
1. **Requested listing**
	1. The submission sought the following listing:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name, Restriction,****Manner of administration and form** | **Max.****Qty (Packs)** | **№.of****Rpts** | **DPMQ** | **Proprietary Name** |
| lixisenatide injection, 10 micrograms/0.2 mL, 14 unit doses (&) 20 micrograms/0.2 mL, , 14 unit doses | ‡1 | 0 | '''''''''''''''''''''''''''''''''''''''''' ''''''''''''''''' | Lyxumia Treatment Initiation Pack  |
| injection, 20 micrograms/0.2 mL, 2x14 unit doses | 1 | 5 | ''''''''''''''''''''''''''''''''''''''''''' ''''''''''''''''' | Lyxumia |

|  |
| --- |
| Authority required (STREAMLINED)**Diabetes mellitus type 2****Clinical criteria:**The treatment must be in combination with insulin,ANDPatient 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; ORPatient 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.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.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.Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or(b) Had red cell transfusion within the previous 3 months.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. |

* 1. The submission sought listing on a cost minimisation with rapid-acting/short-acting components of basal-bolus insulin regimens and premixed insulin.
	2. The ESC noted potential wastage in the requested listing when patients develop side effects and prescribers decide to use the lower dose for a longer period of time.

*For more detail on PBAC’s view, see Section 7 “PBAC Outcome”*

1. **Background**
	1. Lixisenatide was TGA registered on 10 April 2013 for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with metformin, metformin and sulphonylurea, basal insulin and metformin, basal insulin and sulphonylurea when these, together with diet and exercise, do not provide adequate glycaemic control.
	2. This was the PBAC’s first consideration of lixisenatide.
2. **Clinical place for the proposed therapy**
	1. The submission proposed lixisenatide as an alternative to the addition of bolus insulin or a switch to premixed insulin in patients requiring intensification of initial insulin therapy. This is depicted below in the bottom right hand corner. The dual and triple therapy depictions (3rd row of boxes) relate to the submission of Agenda Item 5.9):

HbA1c > 7%

HbA1c > 7%

HbA1c > 7%

HbA1c > 7%

HbA1c > 7%

Premix insulin

Switch to premix

insulin

**lixisenatide plus basal insulin**

Add

**lixisenatide**

 to ongoing basal

therapy

Basal/bolus insulin

Add bolus insulin to ongoing

basal therapy

Single Therapy

Metformin or a

sulphonylurea

Dual Therapy

Metformin plus a sulphonylurea

Intolerant or

contraindicated

Dual Therapy

Metformin + a gliptin, TZD, SGLT2

or GLP-1 agonist (exenatide or  **lixisenatide)**

Or sulphonylurea + a gliptin, TZD or exenatide

Triple Therapy

Metformin + a sulphonylurea + pioglitazone

or a GLP-1 agonist (exenatide or

**lixisenatide)**

Insulin therapy

Initiate insulin therapy

± one or more of the

following: metformin, pioglitazone,

sulphonylurea, acarbose

* 1. The ESC noted that there is significant use of exenatide in combination with insulin outside current PBS restrictions, and that this use may reflect a clinical need to reduce insulin requirements particularly in patients with high levels of insulin resistance and weight gain on insulin. Lixisenatide may be preferred to exenatide in this setting due to once daily dosing.

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

1. **Comparator**
	1. The submission proposed rapid-acting/short-acting components of basal-bolus regimens and premixed insulin as the comparators. The ESC advised that these were appropriate. The ESC also noted that there were other potential comparators: pioglitazone, exenatide, sulfonylureas and optimisation of basal insulin.

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

1. **Consideration of the evidence**

***Sponsor hearing***

* 1. There was no hearing for this item.

***Consumer comments***

* 1. The PBAC noted that no consumer comments were received for this item under agenda item 5.8. However, the PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website but received under agenda item 5.9. The comments described a range of benefits of treatment with lixisenatide including the ability to use smaller insulin doses, which in turn means less chance of experiencing hypoglycaemia and less weight gain. Comment was also made that lixisenatide offers an excellent next step when intensifying therapy after oral agents have failed.

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

***Clinical trials***

* 1. No head-to-head studies were available. The submission relied on a complex series of indirect analyses as follows:
* Indirect comparison of lixisenatide plus basal insulin (GetGoal-L, GetGoal-DUO 1, GetGoal-L-Asia) versus basal-bolus regimen (Owens 2011), using basal insulin as a common reference;
* Indirect comparison of lixisenatide plus basal insulin (GetGoal-L, GetGoal-DUO 1, GetGoal-L-Asia) versus premixed insulin (Ligthelm 2011, Robbins 2007), using basal insulin as a common reference; and
* Two-step indirect comparison using the results of the indirect comparison of lixisenatide plus basal insulin (GetGoal-L, GetGoal-DUO 1, GetGoal-L-Asia) versus premixed insulin (Ligthelm 2011, Robbins 2007) using basal insulin as the first common reference, to inform the second indirect comparison of lixisenatide plus basal insulin versus basal-bolus regimen (Rosenstock 2008), using premixed insulin as the second common reference.
	1. Details of the trials presented in the submission are shown in the table below.

**Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
| --- | --- | --- |
| Lixisenatide + basal insulin vs. placebo + basal insulin |
| GetGoal-L | A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin. | 8 September 2011 |
| Riddle | Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). | *Diabetes Care* 2013; 36(9): 2489-96 |
| GetGoal-DUO 1 | A randomized, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week double-blind treatment period assessing the efficacy and safety of lixisenatide in patients with Type 2 diabetes insufficiently controlled with insulin glargine and metformin. | 2 May 2012 |
| Riddle | Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). | *Diabetes Care* 2013; 36(9): 2497-503 |
| GetGoal-L-Asia | A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea  | 27 July 2011 |
| Seino | Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). | *Diabetes, Obesity and Metabolism* 2012; 14(10): 910-917. |
| Basal-bolus regimen vs. basal insulin |
| Owens  | Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: A 6-month 'proof-of-concept' study.  | *Diabetes, Obesity and Metabolism* 2011; 13(11): 1020-1027.  |
| Premixed insulin vs. basal insulin |
| Ligthelm  | A comparison of twice-daily biphasic insulin aspart 30/70 and once-daily insulin glargine in persons with type 2 diabetes mellitus inadequately controlled on basal insulin and oral therapy: A randomized, open-label study. | *Endocrine Practice* 2011; 17(1): 41-50. |
| Robbins  | Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: A multinational, 24-week, randomized, open-label, parallel-group comparison.  | *Clinical Therapeutics* 2007; 29(11): 2349-2364. |
| **Basal-bolus regimen vs. premixed insulin** |
| Rosenstock  | Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy.  | *Diabetes Care* 2008; 31(1): 20-25. |

Source: Table B.2.2 (pp20-2) of the submission

* 1. Overall the ESC considered that there were some issues surrounding the comparability of the trial population to the PBS context (GetGoal-L-Asia) as well as the lack of evidence quantifying the numerical differences across the common reference arms. The ESC noted differences in race, BMI and insulin doses/duration across the lixisenatide trials.
	2. The ESC further noted the relatively short duration for the trials and questioned whether, from a clinical point of view, the extrapolation of treatment effect beyond the trial period was reasonable.
	3. The ESC questioned whether the indirect comparisons were valid, given the lack of exchangeability between trials. There was substantial variation in change in HbA1c across the “common” reference arms. There were also differences in study design, inclusion/exclusion criteria, baseline characteristics, concomitant medicines and interventions; as well as statistically significant heterogeneity across the pooled lixisenatide trials.

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

***Comparative effectiveness***

* 1. The main outcome presented in the submission was change in HbA1c from baseline. This was the primary outcome for the majority of the included trials. The exceptions were Owens (2011) (proportion of patients achieving HbA1c <7%) and Robbins (2007) (HbA1c at endpoint). The PBAC had previously accepted this main outcome (HbA1c measurement) in assessment of products for diabetes.
	2. Results of the mean change in HbA1c (%) from baseline from the presented trials are summarised in the table below.

**Mean change in HbA1c (%) from baseline (SD)**

| Trial ID | Lixisenatide + basal insulin | Basal insulin  | Premixed insulin | Basal-bolus regimen | Mean difference (95% CI) |
| --- | --- | --- | --- | --- | --- |
| GetGoal-L24 wk | -0.742 (0.979)n=304 | -0.38 (0.979)n=158 | – | – | -0.36 (-0.55, -0.17) |
| GetGoal-DUO 1 24 wk | -0.'''''''''' '''''''''''''n=215 | -0.''''' '''''''''''''''n=221 | – | – | -0.32 '''''''''''''''' '''''''''''''' |
| GetGoal-L-Asia 24 wk | '''''''''''''''' '''''''''''''''''''''''''''' | ''''''''''' '''''''''''''''''''''''''''' | ''' | ''' | '''''''''''' ''''''''''''''' '''''''''''''' |
| Meta-analysis of lixisenatide +basal insulin vs basal insulin (Chi-square: P=0.0002; I2 = 88%) | ''''''''''' '''''''''''''' ''''''''''''''' |
| Owens (2011)3 mth | – | -0.11 (0.603)n= 57 | – | -0.37 (0.603)n= 49 | -0.26 (-0.49, -0.03) |
| Comparison basal-bolus regimen vs basal insulin  | -0.26 (-0.49, -0.03) |
| Ligthelm (2011)24 wk | – | -1.2 (1.05)n=127 | -1.26 (1.05)n=132 | – | -0.06 (-0.32, 0.20) |
| Robbins (2007)24 wk | – | -0.4 (0.9)n=146 | -0.7 (0.9)n=151 | – | -0.30 (-0.50,- 0.10) |
| ''''''''''''''''''''''''''''''' ''''' '''''''''''''''''''''' '''''''''''''''' '''''' ''''''''''''' '''''''''''''''' ''''''''''''''''''''''''''' '''''''''''''''''' '''' '''' ''''''''''''' | ''''''''''' '''''''''''''''' ''''''''''' |
| Rosenstock (2008)24 wk | – | – | -1.87 (0.7)n=150 | -2.09 (0.7) n=147 | -0.22 (- 0.38, -0.07)a |
| Comparison of basal-bolus regimen vs premixed insulin  | -0.22 (- 0.38, -0.07)a |
| 1 step: lixisenatide+ basal insulin vs basal-bolus (one dose) via basal insulin | '''''''''''''' ''''''''''''''' '''''''''''' |
| 2-step: lixisenatide+ basal insulin vs basal-bolus ( 3 doses) via basal & premixed insulin | '''''''''''' '''''''''''''' ''''''''''''' |
| 1-step: lixisenatide+ basal insulin vs premixed insulin via basal insulin | ''''''''''' '''''''''''''''' '''''''''''''' |

Source: Table B(i).6.1 of the commentary

Abbreviations: CI, confidence interval; SD, standard deviation; wk, week

a The 90% CI inaccurately used as a 95% CI. This error does not affect the conclusion of the main analysis.

Note: Some of the SD and the mean change from baseline were synthesised in the submission. Some data could not be verified, but these discrepancies do not change the conclusions.

* 1. There were statistically significantly larger reductions in HbA1c with lixisenatide compared to placebo, on the background of basal insulin and oral diabetes medicines, across the GetGoal trials. The treatment effect on HbA1c with lixisenatide plus basal insulin versus basal insulin was -0.88 (-1.12, -0.65) in the GetGoal-L-Asia trial, which is consistent with significant improvement in this population if a MCID of 0.4% is applied. The point estimates of the difference for GetGoal-L of -0.36% and GetGoal-DUO 1 of -0.32% were smaller than the nominated MCID of 0.4%. The PBAC had previously raised concerns regarding the clinical significance of a difference of 0.33%. (Liraglutide PSD November 2010 and November 2011).
	2. The submission concluded that lixisenatide plus basal insulin is non-inferior to the comparators as the upper limits of the 95% CI of all three indirect comparisons of lixisenatide were less than the nominated minimal clinically important difference (MCID) of 0.4%. The indirect analyses may not have been valid given the lack of exchangeability of the trials. The sponsor acknowledged in the concurrent dual and triple therapy submission that more recent guidance suggests that a non-inferiority margin of 0.3% may be more appropriate. Non-inferiority could be concluded for the two-step indirect comparison of lixisenatide plus basal insulin versus basal-bolus regimen (three bolus doses) using a 0.3% non-inferiority margin.
	3. The ESC noted that using the methods described, statistical comparative effectiveness was demonstrated. However, the ESC questioned whether the results would be replicated in clinical practice as trials often mandate rigid treatment protocols while clinical practice may not. There is considerable complexity with insulin dosing in clinical practice where the insulin doses for individuals increases over time.

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

***Comparative harms***

* 1. No comparative safety data were presented in the submission.
	2. The common adverse events associated with lixisenatide were gastrointestinal disorders (e.g. nausea, vomiting), and hypoglycaemia when used in combination with basal insulin.
	3. The risk of hypoglycaemia appeared higher when lixisenatide is used in combination with basal insulin and a sulfonylurea. Data deficiencies precluded a meaningful indirect analysis of hypoglycaemic events of lixisenatide versus the comparators. There were limited long-term safety data for lixisenatide.
	4. A summary of the key adverse events in the randomised trials is shown in the table below:

**Summary of key adverse events in the randomised trials; n with event (%)**

|  | **GetGoal-La** | **GetGoal-DUO 1** | **GetGoal-L-Asia** |
| --- | --- | --- | --- |
|  | **Lixisenatide****N=328**  | **Placebo****N=167** | **Lixisenatide****N=223**  | **Placebo****N=223** | **Lixisenatide** **N=154** | **Placebo****N=157** |
| Treatment-emergent AE  | '''''''''' ''''''''''''''' | '''''''''' ''''''''''''' | 178 (79.8) | 152 (68.2) | 137 (89.0) | 110 (70.1) |
| Serious TEAE | '''''' '''''''''''''' | ''''''' ''''''''''''' | 17 (7.6) | 10 (4.5) | 10 (6.5) | 9 (5.7) |
| TEAE leading to death | '''' ''''''''''' | ''' '''''''''' | 0 | 2 (0.9) | 0 | 1 (0.6) |
| TEAE leading to discontinuation | '''''' '''''''''''''' | ''''' '''''''''''' | ''''' '''''''''' | 8 (3.6) | 14 (9.1) | 5 (3.2) |
| **Adverse events of interest** |  |  |  |  |  |  |
| *Gastrointestinal disorders* | *''''''''' '''''''''''''* | *'''''' '''''''''''''''* | *''''' '''''''''''''''* | *36 (16.1)* | *94 (61.0)* | *23 (14.6)* |
| - Nausea | '''''' ''''''''''''''' | '''''' '''''''''''' | ''''''' '''''''''''''' | 11 (4.9) | 61 (39.6) | 7 (4.5) |
| - Vomiting | ''''' ''''''''''' | ''' '''''''''''' | ''''' ''''''''''' | 3 (1.3) | 28 (18.2) | 3 (1.9) |
| - Diarrhoea | '''''' ''''''''''''''' | '''''' '''''''''' | ''''' '''''''''' | 7 (3.1) | 10 (6.5) | 4 (2.5) |
| Hypoglycaemia | ''''''''' '''''''''''''' | '''''' ''''''''''''' | '''''' ''''''''''''''' | 43 (19.3) | 67 (43.5) | 37 (23.6) |
| - Symptomatic hypoglycaemia | '''''''''' ''''''''''''''' | ''''' '''''''''''' | 50 (22.4) | 30 (13.5) | 66 (42.9) | 37 (23.6) |
| - Severe hypoglycaemia | ''' ''''''''''' | '''' ''''''''''' | 1 (0.4) | 0 (0) | '''' '''''''' | ''' ''''''' |
| Injection site reactions | ''' '''''''''' | ''' '''''''''''' | 15 (6.7) | 5 (2.2) | 2 (1.3) | 2 (1.3) |
| Adjudicated allergic reactionb | ''''' ''''''''''' | ''' ''''''''''' | 3 (1.3) | 1 (0.''''' | '''' '''''''''' | ''' ''''''' |

Source: Tables B.6.3 (p49), B.6.4 (p50), B.6.5 (p51) and B.6.6 (p53); pp50-3 of the submission. Additional data extracted from the individual CSRs.

Abbreviations: AE, Adverse event; TEAE, treatment-emergent adverse event

a The submission extracted data for the whole study period. During the main 24-week period, 73.5% of patients in the lixisenatide arm versus 68.3% of patients from the placebo arm had TEAEs. Of these, 7.9% in the lixisenatide arm versus 2.4% in the placebo arm discontinued study treatment due to an AE (pp95 and 152 of the CSR).

b The data presented were adjudicated by Allergic Reaction Assessment Committee as possible allergic events.

***Benefits/Harms***

* 1. A summary of the comparative benefits and harms for lixisenatide plus basal insulin versus basal bolus regimens and premixed insulin is presented in the table below.

|  |
| --- |
| **Benefits** |
|  | Active treatment group | Common reference | **Indirect comparison:** **Mean differencea (95% CI)****Lixisenatide vs comparator** |
| n | **Mean ∆ baseline HbA1c** | **SD** | n | **Mean ∆ baseline HbA1c** | **SD** |
| **Mean change from baseline in HbA1c (%) [indirect comparison]** |
| Lixisenatide+ basal insulin vs basal-bolus regimen (one bolus dose) via basal insulin |
| GetGoal-Lb | 304 | -0.742 | 0.979 | 158 | -0.38 | 0.979 | '''''''''''''''''''''''''' '''''''''''' |
| GetGoal-DUO 1b  | 215 | -0'''''''''' | '''''''''' | 221 | -0.40 | '''''''''' |
| GetGoal-L-Asiab  | 146 | -0.773 | '''''''''''' | 154 | 0.11 | '''''''''' |
| Owens (2011) | 49 | -0.37 | 0.603 | 57 | -0.11 | 0.603 |
| Lixisenatide+ basal insulin vs premixed insulin via basal insulin |
| Meta-analysis of GetGoal-L, GetGoal-DUO 1 and GetGoal-L-Asiab | '''''''''''''''''''''''''''' ''''''''''' |
| Ligthelm (2011)c | 132 | -1.26 | 1.05 | 127 | -1.2 | 1.05 |
| Robbins (2007)c | 151 | -0.7 | 0.9 | 146 | -0.4 | 0.9 |
| Lixisenatide+ basal insulin vs basal-bolus regimen ( three bolus doses) via basal insulin then premixed insulin |
| Meta-analysis of GetGoal-L, GetGoal-DUO 1 and GetGoal-L-Asiab | '''''''''''''''''''''''''''' '''''''''''''' |
| Meta-analysis of Ligthelm (2011) and Robbins (2007)c |
| Rosenstock (2008)d | 147 | -2.09 | 0.7 | 150 | -1.87 | 0.7 |
| Harms  |
| Trial | Active treatment group | Common reference | OR(95% CI) | Event rate/100 patientse  | RDf(95% CI) |
| Active treatment group | Common reference |
| Discontinuation due to adverse events [ indirect comparison]i |
| Lixisenatide+ basal insulin vs basal-bolus regimen (one bolus dose) via basal insulin |
| Indirect comparison: Meta-analysis of GetGoal-L, GetGoal-DUO 1 & GetGoal-L-Asiag vs Owens (2011) | NE | - | '''''''''' ''''''''''''''' '''''''''''''' |
| Lixisenatide+ basal insulin vs premixed insulin via basal insulin |
| Indirect comparison: Meta-analysis of GetGoal-L, GetGoal-DUO 1 & GetGoal-L-Asiag vs meta-analysis of Ligthelm (2011) & Robbins (2007)h | ''''''''''' ''''''''''''''' '''''''''''' | - | '''''''''''' ''''''''''''' ''''''''''' |
| Lixisenatide+ basal insulin vs basal-bolus regimen ( three bolus doses) via basal insulin then premixed insulin |
| Indirect comparison: Meta-analysis of GetGoal-L, GetGoal-DUO 1 & GetGoal-L-Asiag vs meta-analysis of Ligthelm (2011) & Robbins (2007)h vs Rosenstock (2008) | ''''''''''' ''''''''''''''' ''''''''''''' | - | ''''''''''' '''''''''''''' '''''''''''''' |

Source: Compiled during the evaluation

Abbreviations: NE, not estimated; OR, odds ratio; RD, risk difference; SD, standard deviation; ∆, change

a Duration of follow-up: 24 weeks, except for Owens (2011) of 3 months

b Chi-square for heterogeneity: P=0.0002; I2 statistic = 88%

c Chi-square for heterogeneity: P=0.15; I2 statistic = 51%

d The 90% CI inaccurately used as a 95% CI. This error does not affect the conclusion of the main analysis.

e Duration of follow-up: 24 weeks except for Owens (2011) of 3 months and GetGoal-L (median 80 weeks)

f The indirect estimate of RD is based on indirect comparisons presented in the submission. However, a more appropriate method to estimate a RD is to apply the relative indirect estimate to a representative baseline risk.

g OR: Chi-square for heterogeneity: P=0.49; I2 statistic = 0%

h OR: Chi-square for heterogeneity: P=0.16; I2 statistic = 50%

i Refer to Table B(i).6.4 (Attachment B)

Note: Some of the SD and the mean change from baseline were synthesised in the submission. Some data could not be verified, but these discrepancies do not change the conclusions.

* 1. On the basis of indirect and multi-step indirect evidence presented in the submission, the comparison of lixisenatide plus basal insulin and comparator drugs (basal-bolus regimens and premixed insulin) resulted in:
* An approximate ''''''''''''''' to ''''''''''''''' reduction in HbA1c over a maximum duration of exposure of 24 weeks. The submission considered that a reduction of 0.4% is clinically significant, and that lixisenatide is equivalent to the comparator drugs.
	1. On the basis of indirect and multi-step indirect evidence presented in the submission, for every 100 patients treated with lixisenatide plus basal insulin in comparison to the comparator drugs (basal-bolus regimens and premixed insulin):
* Approximately 3 to 5 additional patients might stop treatment due to side effects over a median duration of exposure of 24 weeks.

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

***Clinical claim***

* 1. The submission described lixisenatide, in combination with basal insulin and metformin or a sulfonylurea, as clinically equivalent in terms of comparative effectiveness to basal-bolus or premixed insulin regimens (plus metformin or a sulfonylurea).
	2. The submission also described lixisenatide, in combination with basal insulin, as having a similar safety and tolerability profile to basal-bolus or premixed insulin regimens. The submission also claimed that patients treated with lixisenatide experienced significantly lower weight gain.
	3. The ESC considered that the results of the indirect analyses support statistical non-inferiority.

***Economic analysis***

* 1. The submission presented a cost-minimisation analysis. This was consistent with the clinical claim. The appropriateness of the approach was dependent on the acceptance of the clinical claim of equivalence despite the limitations of the presented evidence.
	2. The submission’s estimated equi-effective doses of lixisenatide and rapid-acting insulin were:
* '''''''''''''' mcg of lixisenatide is equivalent to ''''''''''''' units of rapid-acting insulin per day when used in a basal-bolus regimen; and
* '''''''''''''' mcg lixisenatide is equivalent to '''''''''' units of rapid-acting insulin per day when used as premixed insulin.
	1. The estimates were based on the GetGoal trials and Rosenstock (2008). The estimated rapid-acting component for premixed insulin of 61.5 units from Rosenstock (2008) was an overestimate, as 55% of patients switched to evening insulin lispro mix 25/75.
	2. The ESC advised that the estimates of equi-effective doses were unreasonable as the equi-effective dose ('''''''''''''' ''''''''''') is not available in clinical practice (only 20 mcg is), but was not used in the cost-minimisation analysis. Instead, the submission assumed that the average daily cost of treatment with lixisenatide plus basal insulin is equivalent to the average daily weighted cost of basal-bolus and premixed insulin regimens. The sponsor stated that it reserved the right to review the equi-effective price calculations should lixisenatide be recommended for listing
	3. The ESC acknowledged this approach but noted that there was inconsistent insulin pricing between Sections D and E of the submission.
	4. The requested effective price for lixisenatide is summarised in the table below:

**Requested effective price of lixisenatide**

|  | **Premixed insulin** | **Basal-bolus regimen** |
| --- | --- | --- |
| **Bolus** | **Basal** |
| **Cost of insulin based on Rosenstock (2008)** |
| Total insulin dose in units | 123  | 75.92  | 70.08  |
| Average insulin cost per day | $3.66 | $2.23 | '''''''''''' |
| Total average insulin cost per day | $3.66 | '''''''''''''' |
| **Cost of basal insulin based on GetGoal-L and GetGoal-DUO 1**  |
| Average dose of basal insulin used with lixisenatide  | '''''' | - | '''''' |
| Average cost of basal insulin per day | ''''''''''''' | - | '''''''''''' |
| **Cost of insulin accounting for concomitant basal insulin use with lixisenatide**  |
| Proposed daily ex-manufacturer price of lixisenatide in units | ''''''''''''''' | ''''''''''''''' |
| Weighting from relative utilisation (10% Medicare sample) | '''''''''''''''' | '''''''''''''''' |
| Weighted ex-manufacturer cost of lixisenatide per day | ''''''''''''' |
| Requested effective ex-manufacturer price per pack (28 days) | '''''''''''''''' |
| Requested effective DPMQ | '''''''''''''''''' |

Source: Tables D(i).2.1 and D(i).2.2 of the commentary.

* 1. The ESC determined that it was difficult to quantify equi effective dosing. The ESC noted that:
* The escalating doses of insulin required in patients with significant insulin resistance have been adequately incorporated into the calculations
* The dose of rapid acting insulin replaced depends on the underlying long acting dose;
* The dose of insulin used in practice may not actually reduce with the addition of lixisenatide if patients are currently undertreated with insulin. This would affect the cost.
* Individual patient insulin doses increase over time;
* Lixisenatide may have more of an impact on insulin dosing if used as an insulin-sparing agent earlier in the treatment pathway;
* The uptake rates and cost of lixisenatide may be much higher than estimated in the submission due to the issues listed above.
* The availability of lixisenatide may increase the utilisation of insulin in practice, which could be considered a good outcome; and
* There may be insulin wastage in practice with lixisenatide use (e.g. when switching from a premixed insulin).
* Lixisenatide may be added on to current premixed and basal bolus regimes for some patients.
	1. The estimates of equi-effective doses are unreasonable as the equi-effective dose is not available in clinical practice, but are not used in the cost-minimisation analysis. Instead, the submission assumes that the average daily cost of treatment with lixisenatide plus basal insulin is equivalent to the average daily weighted cost of basal-bolus and premixed insulin regimens. The sponsor stated that they reserve the right to review the equi-effective price calculations should lixisenatide be recommended for listing.
	2. Overall, the ESC agreed with the Commentary that the basis for the cost-minimisation analysis may not be justified and that the requested effective DPMQ for lixisenatide is a likely overestimate. The ESC further noted that the effective DPMQ is highly sensitive to the assumed insulin use that would be offset by the use of lixisenatide.
	3. The drug cost/patient/year for lixisenatide was calculated to be $1,132.52, assuming full compliance and not accounting for patient co-payments. This compared with $957.41 for rapid-/short-acting insulin; and $829.57 for premixed insulin adjusted for the concomitant basal insulin use with lixisenatide.

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

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

* 1. This submission was not considered by DUSC.
	2. The submission used a market share approach to estimate the utilisation and financial implications associated with the requested PBS listing of lixisenatide in combination with insulin.
	3. The likely number of lixisenatide patients per year was estimated in the submission to be ''''''''''''''' in Year 5, at an estimated net cost per year to the Government of '''''''''''''''''''''''' in Year 5. The submission’s estimates of PBS usage and financial implications are summarised in the table below:

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|  | **'''''''''' '''** | **''''''''' '''** | **''''''''' '''** | **''''''''' ''** | **'''''''''' '''** |
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Source: Section E\_\_Lixisenatide\_PBAC July\_2014\_09MAR14\_BI

*Note: Numbers in italics corrected during the evaluation.*

*a The number of eligible patients from rapid/short-acting insulin, premixed insulin, pioglitazone and exenatide are estimated separately.*

*b Uptakes rates for individual comparators ranged between ''''''''''' and ''''''''''' in Year 1, increasing to between 8.5% and 30% by Year 5.*

c Assuming ''''''''''''' scripts per patient per year as estimated by the submission.

* 1. The ESC acknowledged the pre-sub-committee response (p4, 6) identification of two errors in the financial estimates including the use of five year data as one year data and the application of the proportion to the wrong population for pioglitazone. The addition of the table below provides an update to the overall net cost to the Government.

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* 1. The ESC noted that it is difficult to tie pricing to a complex restriction and suggested that it may be more appropriate to base pricing on exenatide (an already listed GLP-1 analogue). The ESC further noted the high sensitivity to a change in uptake rates. Hence the ESC considered that the financial estimates were inadequately justified.

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

1. **PBAC Outcome**
	1. The PBAC rejected the request to list lixisenatide for use in combination with insulin on the basis that the clinical place of glucagon-like peptide-1 drugs in type 2 diabetic patients requiring insulin therapy is yet to be established and therefore the appropriate comparator is not only titrated insulin. The basis for the cost minimisation analysis of lixisenatide compared to uptitrated insulin was therefore not accepted. Additionally, the trial based insulin dosage regimens used in the comparison were unlikely to be to be replicated in practice.
	2. The PBAC noted that the requested PBS listing was for use in combination with insulin but that the TGA registered indications for lixisenatide require that lixisenatide also be used in combination with either metformin or a sulfonylurea when lixisenatide is used in combination with insulin. The PBAC further noted that whilst use of the word ‘basal’ in front of ‘insulin’ in the restriction would further be more technically correct, the PBAC did not consider that this would be strictly adhered to by prescribers and noted that it would not be auditable by the Department of Human Services.
	3. The PBAC noted that while the evaluation and ESC considered that rapid/short acting components of basal-bolus regimens and premixed insulins may be appropriate comparators for lixisenatide, the PBAC agreed that they may not be the only relevant comparators. Given that lixisenatide, when used in combination with insulin, must be used also in combination with either metformin or a sulfonylurea, the PBAC considered that it was probable that the therapy likely to be most replaced in practice by lixisenatide (in combination with insulin and metformin/sulfonylurea) would be a treatment regimen containing insulin plus metformin/sulfonylurea plus a non-insulin drug. The PBAC noted in particular that a DUSC February 2013 analysis in a concessional cohort found that approximately 16% of regimens with exenatide, another GLP-1 agonist, included use with insulin despite exenatide not being PBS listed for use in triple therapy with insulin.
	4. The submission’s contention that exenatide is not a comparator as it is not PBS-listed for use in combination with insulin, and is not commonly used as add-on therapy with insulin, was not accepted by the PBAC. The PBAC noted that a comparator does not necessarily need to be PBS listed to be the therapy most likely to be replaced in practice the most. The PBAC observed that as a class of drugs, glucagon-like peptide-1 agonists have only recently been developed and that their role in the management of type 2 diabetic patients requiring treatment progression to insulin use was unclear at this stage. Ideally, the PBAC considered that the PBS listing of lixisenatide should align and reflect the clinical place in therapy that all glucagon-like peptide-1 agonists have in the management of type 2 diabetes and the clinical place is not yet clear.
	5. The PBAC considered the contention in the pre-PBAC response that pioglitazone is also not a valid comparator, due to the low and declining use of pioglitazone for this indication. However, the PBAC noted the estimates of utilisation and costs included in the submission’s assumptions about uptake rates from a range of comparators including a 30% uptake rate of lixisenatide from the exenatide market and a 20% uptake rate from the pioglitazone market in its 5th year of listing. The PBAC considered that this estimate of substitution with exenatide and pioglitazone did not support a comparison against the submission’s nominated comparator of rapid-acting/short-acting components of basal-bolus regimens and premixed insulin.
	6. Overall, the PBAC considered that the clinical place for glucagon-like peptide-1 agonists including lixisenatide in the treatment of type 2 diabetes requiring insulin therapy, needs to be further established.
	7. With regards to comparative efficacy, the PBAC noted that the results of the indirect analyses supported statistical non-inferiority of lixisenatide compared to basal-bolus or premixed insulin regimens (in combination with metformin or a sulfonylurea). However, the PBAC did not accept the submission’s claim of clinical equivalence of lixisenatide to basal-bolus or premixed insulin regimens as the claim of clinical equivalence relied on complex series of indirect analyses that reduced the reliability of the results. The exchangeability of the patient populations between the trials was questionable due to substantial variation in results across the “common” reference arms, differences in study design, inclusion/exclusion criteria, baseline characteristics, concomitant medicines and interventions, as well as statistically significant heterogeneity across the pooled lixisenatide trials. Further, the relatively short duration of the trials meant that the extrapolation of treatment effect beyond the trial period was also potentially unreliable. The PBAC also agreed with the ESC that the complexity of insulin dosing in practice may mean that the insulin doses used in the trials may not be replicated in practice and therefore the results in HbA1c (%) reduction obtained in the trials may not be reliably replicated in practice.
	8. In terms of comparative harms, the PBAC noted that the common adverse events of lixisenatide are gastrointestinal disorders (e.g. nausea, vomiting) and hypoglycaemia when used in combination with basal insulin. However, the absence of direct comparative safety data presented in the submission did not allow the PBAC to form a firm view on the equivalence of lixisenatide compared to basal-bolus or premixed insulin in terms of harms. The submission’s claim that patients treated with lixisenatide experience significantly lower weight gain was further not accepted by the PBAC as the trial data focused primarily on HbA1c measurements as opposed to changes in patient weight. The PBAC recalled a previous preference (see exenatide Public Summary Document, July 2007) for evidence derived from studies that are specifically designed to capture changes in weight loss or quality of life over the long term if such claims are to be made.
	9. As the PBAC was unconvinced that insulin is the most appropriate comparator, the PBAC did not accept the basis for the cost-minimisation analysis presented in the submission. The PBAC further noted the difficulty in estimating the equi-effective dosing between lixisenatide and insulin due to the complexity of insulin dosing in practice, which in turn would have affected the submission’s estimates of drug usage and financial implications.
	10. The PBAC considered the submission’s 10% sampling of Medicare Australia claims data to estimate the extent of use of insulin products in practice had some merit but noted several limitations with this approach. The PBAC noted that that there were no analyses specifically for patients treated with concomitant basal and bolus insulin which limited the applicability of the estimated average daily basal and bolus insulin to the proposed PBS population (some patients are on basal insulin or bolus insulin alone). Additionally, some of the patients in the Medicare Australia sample were unlikely to be suitable for lixisenatide, (e.g. those requiring intensive insulin therapy and those who are not on concomitant oral diabetes medicines – specifically metformin and/or a sulfonylurea). As a result, the PBAC was still unclear on what doses of insulin are being used in practice and therefore likely to be replaced by lixisenatide.
	11. The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

1. **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.

1. **Sponsor’s Comment**

 Whilst the sponsor is disappointed by the PBAC’s decision Sanofi remains committed to working with the PBAC to enable people with diabetes access to Lyxumia.