

**5.9 LIXISENATIDE,
10 microgram/0.2 mL injection, 14 unit doses (&
20 microgram/0.2 mL injection, 14 unit doses,
Lyxumia[®] treatment initiation pack**

**LIXISENATIDE,
20 microgram/0.2 mL injection, 2 x 14 unit doses,
Lyxumia[®], Sanofi-Aventis Australia Pty Ltd**

1 Purpose of Application

- 1.1 The major submission sought an Authority Required (STREAMLINED) listing for the treatment of diabetes mellitus type 2 in patients who meet certain criteria as follows:
(i) dual therapy in combination with metformin; and
(ii) triple therapy in combination with metformin and a sulphonylurea.
- 1.2 It was noted that an Authority required (STREAMLINED) listing for lixisenatide was also sought at this meeting for use as triple combination therapy with basal insulin and either metformin or a sulphonylurea in type 2 diabetes (see agenda item 5.8).

2 Requested listing

- 2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max Qty (Packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name
LIXISENATIDE				
lixisenatide 10 micrograms/0.2 mL, injection, 14 unit doses (& lixisenatide 20 micrograms/0.2 mL, injection, 14 unit doses	‡1	Nil	██████████	Lyxumia Treatment Initiation Pack
lixisenatide, 20 micrograms/0.2 mL, injection, 2 x 14 unit doses	1	5	██████████	Lyxumia
*effective price; proposed published price = ██████████				

The submission proposed the following restriction for dual therapy with metformin:

Authority required (STREAMLINED)

Indication: Diabetes mellitus type 2

Clinical criteria:

The treatment must be in combination with metformin;

AND

Patient must have a contraindication to a combination of metformin and a sulphonylurea; OR

Patient must not have tolerated a combination of metformin and a sulphonylurea,

AND

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 either metformin or a sulphonylurea; 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 either metformin or a sulphonylurea.

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.

The submission proposed the following restriction for triple therapy with metformin and a sulphonylurea:

Authority required (STREAMLINED)

Indication: Diabetes mellitus type 2

Clinical criteria:

The treatment must be in combination with metformin,
AND

The treatment must be in combination with a sulfonylurea,
AND

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 maximally tolerated doses of metformin and a sulfonylurea; 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 maximally tolerated doses of metformin and a sulfonylurea.

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.

- 2.2 Listing was sought on a cost minimisation with exenatide (twice daily).
- 2.3 It was noted that lixisenatide is not TGA-approved for use with a sulfonylurea alone, due to a lack of evidence in an adequate population sample size. The ESC noted that this nuance in lixisenatide's TGA registered indications compared to exenatide's may not be immediately obvious to physicians.

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

3 Background

3.1 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.

3.2 This was the PBAC's first consideration of lixisenatide.

4 Clinical place for the proposed therapy

- 4.1 The submission proposed that lixisenatide would substitute for current use of exenatide when used in dual therapy with metformin and when used in triple therapy with metformin and a sulfonylurea among patients with Type 2 diabetes.

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

5 Comparator

- 5.1 The submission nominated exenatide (twice daily). This was the appropriate comparator, given that positive PBAC recommendations for liraglutide and exenatide once weekly were not effective at the time of the PBAC’s consideration of the submission.

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 health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described a benefit of treatment with lixisenatide as allowing a smaller insulin dose to be administered which in turn leads to the potential for less hypoglycaemia and less weight gain to be experienced by a patient.

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

Clinical trials

- 6.3 The submission was based on direct and indirect comparisons:
- Dual therapy: One head-to-head randomised trial comparing lixisenatide to exenatide, in combination with metformin (GetGoal-X); and
 - Triple therapy: Indirect comparisons of lixisenatide (subgroup from GetGoal-S) versus exenatide (Kendall 2005; exenatide 5 mcg twice daily and 10 mcg twice daily) using placebo as the common reference, in combination with metformin and a sulfonylurea.
- 6.4 An additional lixisenatide trial (in combination with metformin and/or a sulfonylurea), GetGoal-M-Asia, was excluded from the main analysis for triple therapy on the basis that the trial is not directly representative of the proposed PBS population (Asian population only). This approach was inconsistent with the inclusion of GetGoal-L-Asia (Asian population only) in the main analyses of the concurrent lixisenatide submission for use in combination with insulin.
- 6.5 A summary description of the published trials presented in the submission is shown in the table below.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
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Trial ID/First Author	Protocol title/ Publication title	Publication citation
Lixisenatide vs exenatide (dual therapy with metformin)		
GetGoal-X	A randomized, open-label, active-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 versus exenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin (EFC6019)	18 August 2011
Rosenstock	Efficacy and safety of lixisenatide once daily versus exenatide twice daily in Type 2 diabetes inadequately controlled on metformin	<i>Diabetes Care</i> 2013; 36: 2945-2951
Lixisenatide vs placebo (dual/triple therapy with metformin and/or sulfonylurea)		
GetGoal-S	A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea (EFC6015)	1 September 2011
Rosenstock	Beneficial effects of once-daily lixisenatide on overall and postprandial glycaemic levels without significant excess of hypoglycaemia in Type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S)	<i>Journal of Diabetes and its Complications</i> 2014; 201; 28(3): 386–392
GetGoal-M-Asia	Efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus insufficiently controlled by metformin (with or without sulfonylurea): a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with 24-week treatment period (EFC11321)	12 July 2012
Pan	Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: A randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia)	<i>Diabetes/Metabolism Research and Reviews</i> 2014; doi: 10.1002/dmrr.2541. [Epub ahead of print]
Lixisenatide vs placebo (various background therapies)		
ACT6011 Lorenz	Effects of lixisenatide once daily on gastric emptying in type 2 diabetes - relationship to postprandial glycaemia	<i>Regulatory Peptides</i> 2013; 185:1-8
Exenatide vs placebo (dual/triple therapy with metformin and/or sulfonylurea)		
Lu	Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus	<i>Journal of the Formosan Medical Association</i> 2013; 112(3):144-50
Gao	Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea	<i>Diabetes Research and Clinical Practice</i> 2009; 83(1):69-76
Apovian	Effects of exenatide combined with lifestyle modification in patients with Type 2 diabetes	<i>The American Journal of Medicine</i> 2010; 123: 468.e9-468.e17
Kendall	Effects of exenatide (Exendin-4) on glycaemic control over 30 weeks in patients with Type 2 diabetes treated with metformin and a sulphonylurea	<i>Diabetes Care</i> 2005; 28: 1083-1091
Klonoff	Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years	<i>Current Medical Research and Opinion</i> 2008; 24(1):275-86

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Mari	Mathematical modelling shows exenatide improved beta-cell function in patients with type 2 diabetes treated with metformin or metformin and a sulphonylurea	<i>Hormone and Metabolic Research</i> 2006; 38(12):838-44
Exenatide vs placebo (various background therapies)		
Chaudhuri	Exenatide exerts a potent anti-inflammatory effect	<i>Journal of Clinical Endocrinology and Metabolism</i> 2012; 97(1):198-207
Fineman	Effect on glycaemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulphonylurea treatment in patients with type 2 diabetes	<i>Diabetes Care</i> 2003; 26(8):2370-2377
Gejl	Exenatide alters myocardial glucose transport and uptake depending on insulin resistance and increases myocardial blood flow in patients with type 2 diabetes	<i>Journal of Clinical Endocrinology and Metabolism</i> 2012; 97(7):E1165-E1169
Kadowaki	Exenatide exhibits dose-dependent effects on glycaemic control over 12 weeks in Japanese patients with sub optimally controlled type 2 diabetes	<i>Endocrine Journal</i> 2009; 56(3):415-24
Linnebjerg	Effect of exenatide on gastric emptying and relationship to postprandial glycaemia in type 2 diabetes	<i>Regulatory Peptides</i> 2008; 151(1-3):123-9
Wu	Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus	<i>Diabetes Technology and Therapeutics</i> 2011; 13(2):143-83

6.6 A systematic review of lixisenatide with a broader evidence base was located during the evaluation (Schmidt et al. 2014) but that this review had not yet been published.

6.7 The evaluation further identified that an unpublished systematic review and mixed-treatment comparison of GLP-1 receptor agonists had been included in the sponsor's submission to the All Wales Medicines Strategy Group. This was not included in the submission to the PBAC. Given the limitations of the evidence base presented in the submission, the evaluation considered that a broader approach may have provided additional supportive information. It was noted that the pre-sub-committee response (PSCR) (p.4) discounted this review by contending that it "...included a number of comparisons that were not relevant to the requested PBS indication and included comparisons not relevant to the Australian market."

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

Comparative effectiveness

6.8 The primary outcome measured in all trials was the mean change in HbA1c (%) from baseline.

6.9 Direct comparison: Lixisenatide vs. exenatide

The results of GETGOAL-X (dual therapy with metformin) are shown in the table below.

Mean change in HbA1c (%) from baseline to Week 24 in GETGOAL-X (dual therapy with metformin)

	Lixisenatide 20 mcg daily + metformin	Exenatide 10 mcg twice daily + metformin
Primary outcome: mITT population	N=295	N=297
Baseline mean (SD)	7.97 (0.82)	7.96 (0.77)
LS mean change (SE)	-0.79 (0.053)	-0.96 (0.054)
LS mean difference lixisenatide vs. exenatide (95% CI)	0.17 (0.033, 0.297)	
Sensitivity analysis: completer population		
Sensitivity analysis: adjusted for rescue medications		

Source: Table B.6.1 of the commentary

Abbreviations: CI, confidence interval; LS, least square; mITT, modified intention-to-treat; SE, standard error

6.10 Non-inferiority of lixisenatide versus exenatide, on a background of metformin, was demonstrated for GetGoal-X as the upper bound of the 95% confidence interval (CI) was less than the pre-specified non-inferiority margin of 0.4%. The submission claimed that equivalence was still consistently demonstrated when applying a more stringent non-inferiority margin of 0.3%, even though the trial was not powered for this non-inferiority margin.

6.11 The ESC considered this claim to be inadequately supported for the following reasons:

- The results suggest that lixisenatide is borderline non-inferior to exenatide using the more stringent non-inferiority margin of 0.3%, and the conclusion of non-inferiority is sensitive to the statistical analyses conducted.
- Exenatide was associated with a numerically larger reduction in HbA1c compared to lixisenatide, and the 95% CI of the difference between arms did not include the null value.

6.12 Indirect comparison: Lixisenatide vs. exenatide using placebo as the common reference

Results from GetGoal-S and Kendall (2005) are shown in the table below:

Indirect comparison of mean change in HbA1c (%) from baseline to Week 24 (triple therapy with metformin and a sulfonyleurea)

Trial	LS mean change HbA1c (SE)			Mean difference (95% CI)
	Lixisenatide	Placebo	Exenatide	
GetGoal-S (subgroup on MET+SU)				
Kendall (2005) Exenatide 5 mcg twice daily	-	+0.17 (0.07) n=247	-0.6 (0.07) n=245	-0.77 (-0.96, -0.58)
Kendall (2005) Exenatide 10 mcg twice daily	-		-0.9 (0.08) n=241	
Indirect estimate of effect lixisenatide vs exenatide 5 mcg twice daily				
Indirect estimate of effect lixisenatide vs exenatide 10 mcg twice daily				
Indirect estimate of lixisenatide vs exenatide using regression analysis to combine exenatide arms				

Source: Table B.6.2 of the commentary

Abbreviations: CI, confidence interval; LS, least square; MET, metformin; SE, standard error; SU, sulfonyleurea

6.13 The submission claimed that there were no statistically and clinically significant differences between lixisenatide versus exenatide when used in triple therapy in combination with metformin and a sulfonyleurea, even with a large variation in placebo response. The ESC considered that this claim was not supported by the results displayed in the table above. The ESC considered that non-inferiority is not statistically demonstrated for the indirect comparisons of lixisenatide versus exenatide 10 mcg twice daily and versus the combined exenatide 5 mcg and 10 mcg twice daily estimate, as the upper bounds of the respective 95% CI exceed both the nominated non-inferiority margin of 0.4% and a more stringent margin of 0.3%. The

ESC noted that non-inferiority of lixisenatide versus exenatide 5 mcg twice daily is statistically demonstrated for the nominated non-inferiority margin of 0.4% or 0.3%.

- 6.14 The submission and PSCR (p.2) justified the use of the combined results using the exenatide 5 mcg twice daily and 10 mcg twice daily arms by noting that patients may be maintained on either dose. The ESC noted that the evaluation questioned whether this is appropriate. Given that there 112,976 PBS prescriptions processed for the 10 mcg strength over a 12 month period between 1 May 2013 to 30 April 2014 compared to 40,894 prescriptions for the 5 mcg strength, the ESC noted that a majority of patients are on the higher strength of exenatide. The ESC considered that the results from the exenatide 5 mcg twice daily arm may underestimate efficacy (and adverse events) seen in practice and so the combined indirect estimate may bias efficacy comparisons in favour of lixisenatide.
- 6.15 Based on the results presented in the indirect comparison, the evaluation observed that the placebo responses in the two trials included are inconsistent and therefore potentially raise doubts over the exchangeability of the included trials. The ESC noted the PSCR's (p.2) observation that GetGoal-S shows that placebo has an improvement in HbA1c control but that "...the placebo group for Kendall (2005) shows a decline in HbA1c control and therefore the full benefit of lixisenatide compared with exenatide may be underestimated" and considered this to be plausible but uncertain.

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

Comparative harms

- 6.16 The most commonly reported adverse events for both lixisenatide and exenatide were gastrointestinal adverse events (e.g. nausea, vomiting and diarrhoea); and hypoglycaemia when used in combination with metformin and a sulfonylurea. The majority of the gastrointestinal events were mild to moderate in intensity. Few severe hypoglycaemic events were reported in the included trials. In GetGoal-X, fewer patients reported nausea and hypoglycaemia in the lixisenatide arm versus the exenatide 10 mcg twice daily arm. There are no direct comparative data for the development of antibodies. There are limited long-term safety data for lixisenatide.
- 6.17 The ESC noted that no formal statistical testing was performed on the observation that fewer lixisenatide-treated patients experienced nausea, hypoglycaemia and symptomatic hypoglycaemic events than exenatide-treated patients in GetGoal-X. The ESC considered that it is therefore unclear whether the numerical differences are statistically significant. The ESC further considered that such results may be an indication of lixisenatide's inferiority to exenatide (i.e. the observation of reduced hypoglycaemic events with lixisenatide might be a reflection of reduced efficacy). The ESC also noted that patients were aware of their treatment allocation which may have biased the reporting of adverse events.
- 6.18 The pre-sub-committee response (p.2) stated that "No claim of superiority has been made with (sic) regarding improvements in quality of life due to upper GI disorders or the risk of severe hypoglycaemia." The ESC considered this approach to the interpretation of the evidence (and subsequent economic analysis) to be reasonable.

Benefits/Harms

- 6.19 A summary of the benefits and harms for lixisenatide and exenatide is shown the table below.

Summary of comparative benefits and harms for lixisenatide and exenatide

Benefits							
Mean change from baseline in HbA1c (%)							
	Lixisenatide			Exenatide			Mean difference^a: Lixisenatide vs exenatide (95% CI)
	n	Mean Δ baseline HbA1c	SD	n	Mean Δ baseline HbA1c	SD	
Lixisenatide versus exenatide (dual therapy with metformin)							
GetGoal-X	295	-0.79	0.91 ^b	297	-0.96	0.93 ^b	0.17 (0.033, 0.297)
	Active treatment group			Common reference			Indirect comparison: Mean difference^a (95% CI) Lixisenatide vs exenatide
	n	Mean Δ baseline HbA1c	SD	n	Mean Δ baseline HbA1c	SD	
Lixisenatide versus exenatide via placebo (triple therapy with metformin and a sulfonylurea)							
GetGoal-S (subgroup on MET+SU)	■	■	■	■	■	■	-
Kendall (2005) Exenatide 5 mcg bd	245	-0.6	1.1	247	+0.17	1.1	lixisenatide vs exenatide 5 mcg bd ■
Kendall (2005) Exenatide 10 mcg bd	241	-0.9	1.24				lixisenatide vs exenatide 10 mcg bd ■
Regression analysis combining exenatide 5 mcg bd & 10 mcg bd							
Harms							
	Lixisenatide	Exenatide	RR^d (95% CI)	Event rate/100 patients^c		RD^d (95% CI)	
				Lixisenatide	Exenatide		
Lixisenatide versus exenatide (dual therapy with metformin)							
Nausea							
GetGoal-X	■	■	■	■	■	■	■
GetGoal-X	■	■	■	■	■	■	■
GetGoal-X	■	■	■	■	■	■	■
Lixisenatide versus exenatide via placebo (triple therapy with metformin and a sulfonylurea)							
Formal indirect comparisons are appropriately not presented							

Abbreviations: bd, twice daily; MET, metformin; NE, not estimated; RD, risk difference; RR, relative risk; SD, standard deviation; SU, sulfonylurea; Δ, change

^a Duration of follow-up: 24 weeks

^b Calculated by multiplying the SE from the ANCOVA model by the square root of the number of patients

^c Duration of follow-up: Median of 80 weeks

^d No formal statistical testing for secondary outcomes as per the CSR. The submission does not present post-hoc statistical testing

6.20 On the basis of direct and indirect evidence presented in the submission, the comparison of lixisenatide and exenatide resulted in:

- An approximate 0.17% to ■ smaller reduction in HbA1c over a maximum duration of follow-up of 24 week. The submission considered that a reduction of 0.4% is clinically significant and that lixisenatide is equivalent to exenatide.

On the basis of direct evidence presented in the submission, for every 100 patients treated with lixisenatide plus metformin in comparison to exenatide plus metformin;

- Approximately 9 fewer patients would have nausea over a median duration of exposure of 80 weeks.
- Approximately 10 fewer patients would have symptomatic hypoglycaemia (low blood sugar level) over a median duration of exposure of 80 weeks.

- Approximately 7 additional patients would have injection site reactions over a median duration of exposure of 80 weeks.

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

Clinical claim

- 6.21 The submission described lixisenatide as clinically equivalent in terms of comparative effectiveness and as having a similar safety and tolerability profile compared with exenatide, on a background of metformin, alone or in combination a sulfonylurea.
- 6.22 The submission also claimed that in the head-to-head trial, fewer patients treated with lixisenatide experienced nausea, hypoglycaemia and symptomatic hypoglycaemic events than patients treated with exenatide. These claims are not statistically supported and therefore the ESC did not accept the overall claim of non-inferiority based on the evidence presented in the submission.
- 6.23 GetGoal-X did not provide conclusive evidence of non-inferiority of lixisenatide versus exenatide, when used in as dual therapy in combination with metformin. The ESC noted that based on the primary efficacy outcome of mean change in HbA1c (%) from baseline (a 0.17 difference favouring exenatide with the upper bound of the 95% confidence interval being 0.297), lixisenatide is non inferior to exenatide using a minimal clinically important difference (MCID) margin of 0.4, the 95% confidence interval does not include the null and so the results of GetGoal-X suggest that exenatide is numerically superior.
- 6.24 The indirect comparison to support the requested triple therapy restriction may not have been reliable given that the patient populations studied in GetGoal-S and Kendall (2005) did not appear to be exchangeable due to differences in baseline characteristics and background therapies. The indirect comparisons further did not provide conclusive evidence of non-inferiority as the upper bound of the 95% confidence intervals for the indirect estimate of lixisenatide versus exenatide 10 mcg twice daily [REDACTED] and indirect estimate of lixisenatide 5 mcg and 10 mcg twice daily combined [REDACTED], exceeded a MCID margin of 0.4.

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

Economic analysis

- 6.25 A cost-minimisation analysis was presented.
- 6.26 The submission noted that exenatide is listed on the PBS subject to a special pricing arrangement and requested a similar special pricing arrangement for lixisenatide. The submission's cost-minimisation analysis was based on an estimated effective ex-manufacturer price of exenatide twice daily, but because the sponsor did not know the exact price of exenatide, it reserved the right to review the requested price for lixisenatide. The Pre-Sub-Committee Response (p.3-4) further indicated an intention by the sponsor to accept a cost-minimisation price to the effective price of exenatide.
- 6.27 The submission's estimates of the equi-effective doses of lixisenatide and exenatide were:
- lixisenatide [REDACTED] mcg daily.

6.28 The submission stated that the equi-effective doses were derived from weighted average final daily doses (shown in the table below) at 24 weeks in GetGoal-X after dose titrations were completed and patients who discontinued were excluded (i.e. at steady state; p91 of the submission). However, the estimates were derived from the safety population of the fixed-dose GetGoal-X trial, and included data from 41 (13%) patients taking lixisenatide and 45 (14.2%) patients taking exenatide who discontinued treatment prior to Week 24. The submission’s approach was inconsistent with that recommended in the PBAC Guidelines (version 4.4, June 2013).

6.29 The submission’s equi-effective dose estimates also assumed a similar dose relativity between dual and triple therapy.

6.30 The submission’s estimate of lixisenatide’s price to achieve cost-minimisation relative to exenatide is shown in the table below.

Requested ex-manufacturer price and DPMQ for lixisenatide [ESC ADV.9, Table 5]

	EMP/mcg	EMP/day	EMP	DPMQ
Listed price for exenatide 5 mcg twice daily	\$0.3504	\$3.50	\$98.10	\$122.66
10 mcg twice daily	\$0.1886	\$3.77	\$105.60	\$131.52
Requested price for lixisenatide 10-20 mcg once daily				
Price of lixisenatide based on estimated effective prices				
Estimated effective price of exenatide 5 mcg twice daily	Not reported			\$35.53
10 mcg twice daily	\$0.0779	\$1.56	\$46.74	\$61.91
Effective price for lixisenatide 10-20 mcg once daily ^b				

Source: Table D.3 of the commentary

Abbreviations: DPMQ, Dispensed price for maximum quantity; EMP, ex-manufacturer price; NR, not reported

^a Calculation of the requested DPMQ for lixisenatide [redacted] could not be reproduced during the evaluation

^b Prices of lixisenatide initiation and maintenance packs based on maintenance pack cost minimisation versus exenatide 10 mcg twice daily

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

Estimated PBS usage & financial implications

6.31 This submission was not considered by DUSC.

6.32 The submission used an estimated effective price for lixisenatide and exenatide (weighted by PBS utilisation data), and insulin glargine in the estimates of the financial implications to government.

6.33 The likely number of prescriptions dispensed per year was estimated in the submission to be [redacted] in Year 5, at an estimated net cost per year to the PBS of [redacted] in Year 5 following substitution for existing PBS-listed drugs. The

- 7.4 The submission's nominated comparator of exenatide (twice daily) was therefore accepted by PBAC.
- 7.5 The PBAC agreed that for the dual therapy indication, the one head-to-head randomised trial comparing lixisenatide to exenatide in combination with metformin (GetGoal-X) did not provide conclusive evidence of non-inferiority of lixisenatide versus exenatide. The PBAC noted that the difference in the mean change in HbA1c (%) from baseline to Week 24 in GETGOAL-X between lixisenatide and exenatide was 0.17% favouring exenatide. For this estimate of a 0.17% difference, the upper limit of the 95% confidence interval was 0.297% and the lower limit was 0.033%. Although the upper limit of the 95% confidence interval did not exceed a more stringent minimal clinically important difference (MCID) margin of 0.3% compared to a MCID margin of 0.4%, the lower limit of the 95% confidence interval (0.033%) did not include the null and so the results of GetGoal-X suggested with a high degree of certainty that lixisenatide is slightly worse than exenatide at lowering HbA1c measurements. Whether this slight inferiority of lixisenatide to exenatide is clinically significant was debatable but the PBAC was not prepared to accept the claim that lixisenatide is non-inferior to exenatide when used in dual therapy treatment based on these results.
- 7.6 The PBAC further considered that for the triple therapy indication, the indirect comparison also did not provide conclusive evidence of non-inferiority of lixisenatide versus exenatide. The PBAC noted that in practice, a greater number of patients are treated with exenatide 10 mcg twice daily than exenatide 5 mcg twice daily and therefore agreed with the ESC that these results are likely to be more reliable than the results for the comparisons against exenatide 5 mcg (twice daily) or a combination of exenatide 5 mcg & 10 mcg. In the indirect comparison of lixisenatide vs. exenatide 10 mcg (twice daily), the difference in mean change in HbA1c (%) from baseline to Week 24 (in triple therapy with metformin and a sulfonylurea) [REDACTED] favouring exenatide. Like the dual therapy results, the lower limit of the 95% confidence interval (0.08%) did not include the null and so the results of the indirect comparison suggested with a high degree of certainty that lixisenatide is worse than exenatide 10 mcg (twice daily) at lowering HbA1c measurements. Further to this, whether a MCID margin of 0.3% or 0.4% is used to determine if the results are clinically significant, the PBAC noted that the upper limit of the 95% confidence interval (0.62%) suggested that lixisenatide may be clinically worse than exenatide 10 mcg (twice daily) when used in the triple therapy setting. Therefore, the PBAC was not prepared to accept the claim that lixisenatide is non-inferior to exenatide when used in triple therapy treatment based on these results.
- 7.7 In terms of comparative safety, it was noted that no formal statistical testing was performed on the observation that fewer lixisenatide-treated patients experienced nausea, hypoglycaemia and symptomatic hypoglycaemic events than exenatide-treated patients in GetGoal-X. The PBAC considered that it was therefore unclear whether the numerical differences were statistically significant and clinically significant. The PBAC agreed with the ESC's concerns that such results may be an indication of lixisenatide's inferiority to exenatide (i.e. the observation of reduced hypoglycaemic events with lixisenatide might be a reflection of reduced efficacy). The PBAC also noted that patients were aware of their treatment allocation which may have biased the reporting of adverse events. For these reasons, the PBAC was yet to accept a claim of non-inferiority of lixisenatide compared to exenatide (twice daily) in terms of safety.
- 7.8 The PBAC considered that any future resubmission would need to particularly address claims regarding lixisenatide's comparative efficacy and safety compared to

exenatide (twice daily). The PBAC's current view is that there is no compelling clinical need for a drug that appears to be slightly inferior to existing therapy. Any resubmission would need to establish a compelling clinical need for lixisenatide therapy if non-inferiority to existing therapy cannot be conclusively demonstrated in a major resubmission.

7.9 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

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.