PUBLIC SUMMARY DOCUMENT
Product: Liraglutide, solution for injection, 6mg/mL, Victoza®
Sponsor: Novo Nordisk Pharmceuticals Pty Ltd.
Date of PBAC Consideration: March 2013

1. Purpose of Application

The re-submission requested an Authority required listing for the treatment of type 2 diabetes as dual combination therapy with metformin or a sulfonylurea in patients for whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated; and as triple combination therapy with metformin and a sulfonylurea.

2. Background

This was the fourth consideration by the PBAC of liraglutide for the requested indication.

Previous submissions based on the claim that liraglutide 1.8 mg per day was superior to exenatide were rejected at the November 2010, July 2011 and November 2011 meetings on the basis of uncertain cost effectivenss. At the July 2011 meeting, the PBAC formed a view that the stastistiscally significant difference of -0.33% change in HbA1c, favouring liraglutide compared to exenatide, was marginally clinically meaningful. However, at the November 2011 meeting, the PBAC considered, based on more recent publications, the difference of -0.33% was of uncertain clinical benefit and rejected the submission on the basis that the claim of superior comparative effectiveness over exenatide was not accepted and highly uncertain cost effectiveness.

Public Summary Documents for the November 2010 and November 2011 considerations are available at:
http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product#JKL

3. Registration Status

On 26 August 2010, liraglutide was registered for the following indication:

As an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

- in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.
- in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.

4. Listing Requested and PBAC's View

Authority Required listing for the treatment of type 2 diabetes as:
1) dual combination therapy with metformin OR a sulfonylurea in patients for whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated;
2) triple combination therapy with metformin AND a sulfonylurea.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The submission proposed that liraglutide would be an additional treatment option to the currently PBS-listed glucagon like peptide (GLP-1) analogues (eg. exenatide) and dipeptidyl peptidase 4 (DPP-4) inhibitors (eg, sitagliptin, vildagliptin, saxagliptin, linagliptin) for patients with type 2 diabetes.

6. Comparator

The re-submission nominated exenatide as the comparator. This was previously accepted by the PBAC.

7. Clinical Trials

The re-submission presented an indirect comparison of liraglutide 1.2 mg daily versus exenatide 10 micrograms twice daily in patients with type 2 diabetes, using placebo as the common comparator. The indirect comparison was based on a meta-analysis of three liraglutide trials in 1,023 patients (LEAD 1, LEAD 2, LEAD 4), previously considered by the PBAC, and ten exenatide trials in 2,605 patients.

Two of the three liraglutide trials assessed the efficacy of liraglutide 1.2 mg in combination with sulfonylurea (LEAD 1) or metformin (LEAD 2). There were no trials available assessing the use of liraglutide 1.2 mg in a triple therapy regimen which were consistent with the requested listing i.e. in combination with a sulfonylurea AND metformin.

The primary outcome in the indirect comparison was change from baseline HbA1c. The PBAC recalled it had previously questioned the relevance of the surrogate outcome, HbA1c % change from baseline, and particularly the clinical significance of small changes in this measure (PBAC Minutes, November 2011) as noted in recent publications[1, 2].

The table below details the published trials and associated reports presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Common Reference: Placebo		
Liraglutide		
LEAD 1 (NN2211-1436)	6 month, DB, DD, R, AC, PG, MC, MN To assess and compare the effect on glycaemic control of once daily administration of three doses of liraglutide (0.6, 1.2 or 1.8mg/day) in combination with glimepiride (2-4mg/day) versus glimepiride monotherapy versus rosiglitazone (4mg/day) and glimepiride combination therapy in subjects with type 2 diabetes	CSR: Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial. 15th February 2008
Marre M et al (2009).	Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements	Diabetic Medicine, 26: 268-278.

[1] Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Bergeonneau C, Kassai B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised control trials. BMJ. 2011;343:1-12

[2] Kilpatrick ES, Bloomgarden ZT, Zimmet PZ. Is haemoglobin A_{1c} a step forward for diagnosing diabetes? BMJ 2009;339:1288-1290

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	in glycaemic and weight control compared with adding rosiglitazone to placebo in subjects with Type 2 diabetes (LEAD-1 SU).	
LEAD 2 (NN2211-1572)	6 month, DB, DD, R, AC, PG, MC, MN To assess and compare the effect on glycaemic control of once daily administration of three doses of liraglutide (0.6, 1.2 or 1.8mg/day) in combination with metformin (1500-2000mg/day) versus metformin monotherapy versus metformin and glimepiride (4mg/day) combination therapy in subjects with type 2 diabetes.	CSR: Liraglutide Effect and Action in Diabetes (LEAD-2): Effect on glycaemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomised, active control, parallel-group, multi-centre, multi-national trial with an 18 months extension period. 5th February 2008
Nauck M et al (2009).	Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination With Metformin, in Type 2 Diabetes: The LEAD (Liraglutide Effect and Action in Diabetes)-2 study	Diabetes Care, 32:84-90
LEAD 4 (NN2211-1574)	26 week, MC, DB, R, PT To assess and compare the efficacy of two doses of liraglutide (1.2 and 1.8mg) in combination with rosiglitazone (8mg/day) and metformin (2000mg/day) versus the combination of rosiglitazone and metformin on glycaemic control after 26 weeks with type 2 diabetes.	CSR: Liraglutide Effect and Action in Diabetes (LEAD 4): Effect on Glycaemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)
Zinman B et al (2009).	Efficacy and Safety of the Human Glucagon-Like Peptide-1 Analog Liraglutide in Combination With Metformin and Thiazolidinedione in Patients with Type 2 Diabetes (LEAD-4 Met + TZD).	Diabetes Care, 32(7):1224-1230
Main Comparator: Exenatide		
Apovian 2010	Effects of Exenatide Combined with Lifestyle Modification in Patients with Type 2 Diabetes.	The American Journal of Medicine, 123(5):468e9-468e17
Buse 2004	Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Sulfonylurea-Treated Patients with Type 2 Diabetes.	Diabetes Care 27(11):2628-2635
Buse 2011	Use of Twice-Daily Exenatide in Basal Insulin-Treated Patients with Type 2 Diabetes.	Annals of Internal Medicine. 154:103-112
DeFronzo 2005	Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients with Type 2 Diabetes.	Diabetes Care. 28:1092-1100
Derosa 2012	Exenatide plus metformin compared with metformin alone on β-cell function in patients with Type 2 diabetes.	Diabetic Medicine 'Accepted Article', doi:10.1111/j.1464-5491.2012.03699.x

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Gao 2009	Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea.	Diabetes Research and Clinical Practice. 83:69-76
Kendall 2005	Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients with Type 2 Diabetes Treated With Metformin and a Sulfonylurea.	Diabetes Care. 28(5):1083-1091
Liutkus 2010	A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. Diabetes,	Obesity and Metabolism. 12:1058-1065
Moretto 2008	Efficacy and Tolerability of Exenatide Monotherapy Over 24 weeks in Antidiabetic Drug-Naïve Patients with Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study.	Clinical Therapeutics. 30(8):1448-1460
Zinman 2007	The Effect of Adding Exenatide to a Thiazolidinedione in Suboptimally Controlled Type 2 Diabetes.	Annals of Internal Medicine. 146:477-485

Abbreviations: AC = active control, DB = double-blind; DD = double dummy; MC = Multi-Centre; MN = multi-national; PG = parallel group; PC = Placebo Controlled; PT = parallel trial; R = Randomized; TB = Triple Blind

8. Results of Trials

The submission presented glycaemic control measured by change from baseline HbA_{1c} as the primary outcome in the indirect comparison for liraglutide 1.2 mg and exenatide 10 micrograms.

The results of change from baseline HbA_{1c} in the indirect comparison of liraglutide 1.2 mg and exenatide 10 micrograms are shown in the table below.

Trial	B/ground Therapy^	Active Treatment Group			Placebo Group			Mean difference vs placebo (95% CI)*
		n	Mean change from baseline HbA_{1c}	SD	n	Mean change from baseline HbA_{1c}	SD	
Liraglutide Trials								
LEAD 1	SU	223	-1.08	1.05	107	0.23	1.03	**-1.31 (-1.55, -1.07)**
LEAD 2	MET	232	-0.97	1.07	120	0.09	0.99	**-1.06 (-1.29, -0.83)**
LEAD 4	MET+ TZD	174	-1.48	0.95	167	-0.54	1.03	**-0.94 (-1.16, -0.72)**
							Meta analyses: Random effects (DerSimon	**-1.10 (-1.31, -0.89)**

							ian-Laird):	
Exenatide Trials								
Apovian 2010	MET /SU / MET+SU	96	-1.21	0.88	98	-0.73	0.89	**-0.48 (-0.72, -0.23)**
Buse 2004	SU	129	-0.86	1.25	123	0.12	1.00	**-0.98 (-1.26, -0.70)**
Buse 2011	Insulin ± MET/ TZD/ MET+TZD	137	-1.74	1.05	122	-1.04	1.01	**-0.70 (-0.95, -0.45)**
DeFronzo 2005	MET	113	-0.78	1.06	113	0.08	1.06	**-0.86 (-1.14, -0.58)**
Derosa 2012	MET	86	-1.20	0.80	85	-0.40	0.66	**-0.80 (-1.02, -0.58)**
Gao 2009	MET ± SU	234	-1.20	0.78	232	-0.40	1.17	**-0.80 (-0.98, -0.62)**
Kendall 2005	MET +SU	241	-0.77	1.24	247	0.23	1.10	**-1.00 (-1.21, -0.79)**
Liutkis 2010	TZD ± MET	111	-0.84	2.11	54	-0.10	1.69	**-0.74 (-1.38, -0.10)**
Moretto 2008	No OAD	76	-0.90	0.87	75	-0.20	0.87	**-0.70 (-0.98, -0.42)**
Zinman 2007	TZD ± MET	121	-0.89	0.99	112	0.09	1.06	**-0.98 (-1.24, -0.72)**
							Meta analyses: Random effects (DerSimonian-Laird):	**-0.81 (-0.91, -0.71)**
Indirect Comparison: Liraglutide 1.2mg vs Exenatide 10µg								**-0.29 (-0.52, -0.06)**

Abbreviations: MET = Metformin; OAD = Oral Anti-diabetic drug; SU = Sulfonylurea; TZD = Thiazolidinedione

Statistically significant greater reductions in HbA_{1c} were observed in the active treatment arm of each of the randomised trials compared to placebo. This was also demonstrated in the meta-analyses for liraglutide 1.2mg and exenatide 10 micrograms versus placebo. Across the placebo arms of the liraglutide and exenatide trials there was a noticeable variation in results for percentage change in HbA_{1c} from baseline (liraglutide: -0.54 to 0.23; exenatide: -1.04 to 0.23).

The results of the indirect comparison suggested that there was a statistically significant reduction (-0.29%, 95% CI: -0.52, -0.06) in estimated mean difference of change from baseline HbA_{1c} for liraglutide 1.2 mg compared with exenatide 10 micrograms, using placebo as the common reference.

The PBAC noted that the background therapies in the liraglutide and exenatide trials were different. The majority of the exenatide trials assessed the use of exenatide as a part of a triple therapy (only 24.6% of patients were on dual therapy) compared with the liraglutide trials in which approximately 66.7% of patients were receiving dual therapy. Additional analyses were conducted during the evaluation comparing only the trials with consistent background therapies and the results are presented in the table below.

Additional analyses conducted comparing liraglutide and exenatide restricted to trials with relevant background therapies

Comparison	Trials included	WMD (95% CI) in HbA_{1c}
Liraglutide 1.2mg od + SU versus exenatide 10µg bd +SU	Lira: LEAD 1 Exenatide: Apovian 2010, Buse 2004	-0.45 (-1.22, 0.33)
Liraglutide 1.2mg od + MET versus exenatide 10µg bd + MET	Lira: LEAD 2 Exenatide: Apovian 2010, DeFronzo 2005, Derosa 2012	-0.22 (-0.45, 0.01)
Liraglutide 1.2mg od + SU or MET versus exenatide 10µg bd +SU or MET	Meta-analyses of the above (i) liraglutide and (ii) exenatide trials	**-0.44** **(-0.76, -0.12)**

Abbreviations: Lira = Liraglutide; MET = Metformin; SU = Sulfonylurea; WMD = Weighted mean difference

The PBAC noted the results of the indirect comparison indicated there were no statistically significant differences in HbA1c reduction between liraglutide and exenatide when only trials assessing the addition of these therapies to SU (WMD=-0.45; 95% CI: -1.22, 0.33) or MET (WMD=-0.22; 95% CI: -0.45, 0.01) were considered. However, when the MET and SU trials were combined, treatment with liraglutide 1.2 mg was associated with a statistically significant greater reduction in HbA1c compared with exenatide 10 micrograms twice daily (WMD=-0.44; 95% CI:-0.76, -0.12).

The most common adverse events reported across the liraglutide and exenatide trials were gastrointestinal in nature and included nausea and vomiting, consistent with safety data previously considered by the PBAC for liraglutide 1.8 mg. In addition, the results of the indirect comparison indicated that there was no statistically significant difference between liraglutide 1.2 mg and exenatide 10 micrograms in the proportion of patients who had treatment emergent nausea. A secondary analysis presented by the resubmission claimed significantly less duration of nausea. The PBAC noted in the product information documents for exenatide and liraglutide, nausea is considered to be transient in nature, and rarely led to withdrawals from the trials. The PBAC also noted the results from the indirect comparison indicated that liraglutide 1.2 mg is similar to exenatide 10 micrograms in terms of withdrawals due to adverse events (OR 0.62; 95% CI: 0.19, 2.00).

The PBAC noted that the consumer comments received in relation to the submission for liraglutide did not appear to make mention of reduction in nausea as a perceived advantage for liraglutide. The consumer comments highlighted fewer injections and weight loss/less weight gain as perceived advantages. The PBAC noted the advice of the clinician during the hearing that patients experiencing nausea associated with exenatide are kknown to skip doses, delay doses, or use exenatide once daily rather than twice daily, in an effort to manage nausea. The clinician advised that 30-35% of patients on exenatide have persistent or ongoing nausea, reduced patient adherence to therapy is not uncommon, and may results in sub-optimal health outcomes.

Overall, the PBAC considered that the difference in rates and duration of nausea was modest, and was not reflected in discontinuation rates or other markers (e.g., antiemetic use).

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed liraglutide 1.2 mg is non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over exenatide 10 micrograms, however claimed significantly less duration of nausea.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a cost-minimisation analysis based on non-inferiority claim for change in HbA1c and fasting plasma glucose, including offsets for cost of needles. In addition, a price premium was requested for one less injection per day, dosing flexibility and reduced duration of nausea compared to exenatide. The re-submission presented results from a Willingness To Pay (WTP) survey as cumulative attributes in determining the value of these additional claimed benefits.

The equi-effective doses were estimated as liraglutide 1.2 mg once daily and exenatide 10 micrograms twice daily. The PBAC accepted these as appropriate.

The PBAC noted that the requested price for liraglutide included a price premium over the cost-minimisation price for the following attributes of liraglutide compared with exenatide:

- one less injection per day;
- administration irrespective of meals;
- reduction in nausea.

The re-submission relied on the study reported by Jendle (2010), who estimated the 'Willingness To Pay' (WTP) for the above attributes to support the requested price premium.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be between 10,000 and 50,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 miilion in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended listing of liraglutide as an Authority required (STREAMLINED) benefit for dual combination therapy with metformin or a sulfonylurea, and as triple combination therapy with metformin and a sulfonylurea on a cost minimisation basis with exenatide. The accepted equi-effective doses are liraglutide 1.2 mg once daily and exenatide 10 micrograms twice daily.

The PBAC considered that the evidence presented in the re-submission supported the claim of non-inferiority of liraglutide 1.2 mg once daily compared with exenatide 10 micrograms twice daily in terms of change in HbA1c. The PBAC noted that the evidence presented also indicated that there was no statistically significant difference in overall adverse events between liraglutide and exenatide. The PBAC therefore accepted the re-submissions'claim of non-inferior effectiveness and safety of liraglutide 1.2 mg daily compared with exenatide

10 micrograms twice daily.

The PBAC considered that the 'Willingness To Pay' (WTP) study presented in the re-submission was not an appropriate basis upon which to justify the requested price. The PBAC did not accept the sponsor's claim of cost-offsets for one less needle per day.

The PBAC considered the re-submission's estimates of usage and cost to the PBS were potentially underestimated and held concerns regarding use of liraglutide at a dose of 1.8 mg daily, a dose for which superiority over exenatide 10 micrograms twice daily had not been accepted.

The PBAC considered that liraglutide is suitable for inclusion in the list of medicines for prescribing by nurse practitioners within collaborative arrangements.

Recommendation:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
liraglutide solution for injection, 6mg/mL in pre-filled pen, 3 mL, 2	1	5	Victoza	NO

Condition/Indication:	Diabetes mellitus type 2
Restriction:	Authority required (STREAMLINED)
Treatment phase:	Dual combination therapy with metformin or a sulfonylurea.
Treatment criteria:	The treatment must be in combination with metformin. OR: The treatment must be in combination with a sulfonylurea.
Clinical criteria:	AND: Patient must not be able to tolerate a combination of metformin and a sulfonylurea or a combination of metformin and a sulfonylurea is contraindicated. AND: Patient must have a glycosylated haemoglobin (HbA1c) greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea. OR: Patient must have, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a two week period prior to initiation of a gliptin, a glitazone or a glucagon-like peptide-1 despite treatment with metformin or a sulfonylurea. AND: The treatment must not be used in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor

	(gliptin).
Prescriber Instructions	The date and level of the HbA1c must be documented in the patient's medical records at the time therapy with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no greater than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances: a) clinical conditions with reduced red blood cell survival, including haemolytic anaemia and haemoglobinopathies and/or b) 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 or a glucagon-like peptide-1, must be documented in the patient's medical records.
Administrative Advice	Liraglutide is not PBS-subsidised as monotherapy. No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

Condition/Indication:	Diabetes mellitus type 2
Restriction:	Authority required (STREAMLINED
Treatment phase:	Triple combination therapy with metformin or a sulfonylurea.
Treatment criteria:	The treatment must be in combination with metformin and a sulfonylurea.
Clinical criteria:	AND: Patient must have a glycosylated haemoglobin (HbA1c) greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea. OR: Patient must have, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a two week period prior to initiation of a gliptin, a glitazone or a glucagon-like peptide-1 despite treatment with metformin or a sulfonylurea. AND: The treatment must not be used in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor (gliptin).

Prescriber Instructions	The date and level of the HbA1c must be documented in the patient's medical records at the time therapy with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no greater than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances: a) clinical conditions with reduced red blood cell survival, including haemolytic anaemia and haemoglobinopathies and/or b) 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 or a glucagon-like peptide-1, must be documented in the patient's medical records.
Administrative Advice	Liraglutide is not PBS-subsidised as monotherapy. No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

13. 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.

14. Sponsor's Comment

Novo Nordisk is pleased to receive a positive PBAC recommendation and looks forward to progressing a PBS listing for liraglutide. Novo Nordisk is however disappointed that cost offsets such as using one needle daily for liraglutide versus two needles daily for exenatide were not accepted. They are further disappointed that patient features regarding once vs twice daily dosing, any time of day dosing and a reduced duration of nausea, were not considered to hold additional value by the PBAC.