PUBLIC SUMMARY DOCUMENT
Product: Liraglutide (rys), injection solution, pre-filled pen, 6 mg per mL, 3 mL, 2 and 3 pen pack, Victoza®
Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request an Authority Required listing for the treatment of type 2 diabetes as:

1) dual combination therapy with metformin or a sulphonylurea in patients for whom a combination of metformin and a sulphonylurea is contraindicated or not tolerated;
2) triple combination therapy with metformin and a sulphonylurea.

2. Background

This was the third consideration by the PBAC of an application to list liraglutide.

At its November 2010 meeting, the PBAC rejected a submission to list liraglutide for the same indications as mentioned above because of an unacceptably high and uncertain cost effectiveness ratio.

For full details, see November 2010 Public Summary Document.

At the July 2011 meeting, the PBAC rejected a minor submission seeking the same indications as mentioned-above on the basis of uncertain cost effectiveness.

3. Registration Status

On 26 August 2010, liraglutide was registered for the following indication:
Liraglutide is indicated 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 sulphonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulphonylurea monotherapy.
- in triple combination, added to metformin and a sulphonylurea in patients with insufficient glycaemic control despite dual therapy.

4. Listing Requested and PBAC's View

Authority required
Dual Combination therapy with metformin or a sulfonylurea.
Initiation of therapy, in combination with either metformin or a sulfonylurea, in a patient with type 2 diabetes who has an HbA1c greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 and in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

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.

Continuation of therapy, in combination with either metformin or a sulfonylurea, in a patient with type 2 diabetes where the patient has previously been issued with an authority prescription for liraglutide.

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.

Patients in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this 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.

NOTE:
Liraglutide is not PBS-subsidised as monotherapy or in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor (gliptin).

Authority required
Combination therapy with metformin and a sulfonylurea.
Initiation of therapy, in combination with metformin and a sulfonylurea, in a patient with type 2 diabetes who has an HbA1c greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite maximally tolerated doses of metformin and a sulfonylurea.

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.

Continuation of therapy, in combination with either metformin and a sulfonylurea, in a patient with type 2 diabetes where the patient has previously been issued with an authority prescription for liraglutide.

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NOTE:
Liraglutide is not PBS-subsidised as monotherapy or in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor (gliptin).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Liraglutide, an injection given once daily, is a glucagon-like peptide 1(GLP-1) mimetic and the submission proposed that the place in therapy is as an add-on treatment option where there is inadequate glycaemic control with either metformin or a sulfonylurea or both.

6. Comparator

The submission nominated exenatide as the comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The basis of the re-submission was one direct randomised comparative trial, which was presented in the previous submission, comparing liraglutide 1.8 mg daily and exenatide 10 µg twice daily (Study 1797) added to metformin, a sulfonylurea or a combination of both in type 2 diabetics.

The current re-submission presented additional data from Study 1797 on patient preferences (Schmidt et al, 2011) and antibody production (Buse et al, 2011).

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Study 1797 (LEAD 6) Buse et al.	Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6).	Lancet 2009; 374: 39–47
Buse et al.	Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents.	Diabetes Care 2010: 33: 1300-1303
Schmidt et al.	Patient-reported outcomes are superior in patients with Type 2 diabetes treated with liraglutide as compared with exenatide, when added to metformin, sulphonylurea or both: results from a randomized, open-label study.	Diabetic Medicine 2011; 28: 715-723
Buse et al.	Liraglutide Treatment Is Associated with a Low Frequency and Magnitude of Antibody Formation with No Apparent Impact on Glycemic Response or Increased Frequency of Adverse Events: Results from the Liraglutide Effect and Action in Diabetes (LEAD) Trials.	Journal of Clinical Endocrinology and Metabolism 2011; 96: 1695-1702
Lee et al.	Results of a model analysis of the cost-effectiveness of liraglutide versus exenatide added to metformin, glimepiride, or both for the treatment of type 2 diabetes in the United States.	Clinical Therapeutics 2010; 32: 1756-1767
Polster et al.	A comparison of preferences for two GLP-1 products – Liraglutide and exenatide - For the treatment of type 2 diabetes.	Journal of Medical Economics 2010: 13: 655-661

8. Results of Trials

The table below summarises the HbA1c change from baseline at Week 26 for Study 1797 (LEAD-6).

HbA1c change from baseline at Week 26 in % (ITT - LOCF)

Liraglutide 1.8mg/day + MET &/or SU N=227			**Exenatide10µg/BD + MET &/or SU N=226**			**LS Mean difference[a] (95% CI)**
Baseline Mean (SD)	**26 weeks Mean (SD)**	**LS Mean change[a] (SE)**	**Baseline Mean (SD)**	**26 weeks Mean (SD)**	**LS Mean change[a] (SE)**	
8.2 (1.0)	7.0 (0.91)	-1.12 (0.08)	8.1 (0.96)	7.3 (1.03)	-0.79 (*0.08*)	-0.33 (-0.47, -0.18)

Abbreviations: BD, twice daily; CI, confidence interval; HbA1c, glycosylated haemoglobin; ITT, intention-to-treat; LOCF, last observation carried forward; LS, least squares; MET, metformin; SD, standard deviation; SE, standard error; SU, sulfonylurea.

[a] ANCOVA model with treatment, country, and previous treatment as fixed effects and baseline value as a covariate. Difference is (liraglutide-exenatide). This compares to the mean change (SD) previously presented in the November 2010 submission.

There were statistically significantly greater reductions in HbA1c from baseline at Week 26 for liraglutide 1.8 mg/day compared to exenatide 10 µg twice daily (LS mean difference -0.33%, 95% CI -0.47%, -0.18%).

As with the July 2011 minor submission, the re-submission provided additional information to support the claim that a 0.33% reduction in HbA1c is clinically relevant, referring to US FDA and EMA draft guidance documents. While considering that this information was contributory to the PBAC's view that the stastistiscally significant difference of 0.33% change in HbA1c, favouring liraglutide compared to exenatide, was marginally clinically meaningful, as expressed in July 2011, the PBAC also noted more recent publications (such as *BMJ 2011;343:d4169, BMJ 2009;339:b4432*) that raised questions again about the clinical significance of small changes in this surrogate endpoint.

The Pre-Sub-Committee Response (PSCR) identified a meta-analysis of the UKPDS, ADVANCE, ACCORD and VDAT studies (Diabetologia. 2009;52:2288-98, *Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al*), which generates more precise estimates of the effects of more-intensive compared with less-intensive glyceamic control on the risk of major cardiovascular events amongst patients with type 2 diabetes. The PSCR highlighted the result of a modestly reduced risk of major macrovascular events with more-intensive glucose control.

During the 26-week trial, there were no major hypoglycaemic events in the liraglutide group and only two patients out of 232 experienced a major hypoglycaemic event in the exenatide group. No statistical analyses were performed owing to the "small" numbers. There were statistically significantly fewer patients with minor hypoglycaemic episodes with liraglutide treatment compared with exenatide treatment.

Similar proportions of patients reported gastrointestinal side effects (45.5% liraglutide and 42.7% exenatide), and specifically nausea (25.5% liraglutide and 28.0% exenatide).

The re-submission described nausea and the gastrointestinal side effects of GLP-1 therapies (exenatide and liraglutide) as usually transient and not serious. The duration of nausea in the maintenance phase of the clinical trial was longer in the exenatide arm compared to the liraglutide arm (median duration of 57 days versus 14 days). The re-submission claimed that the shorter median duration means that "less patients" experienced nausea in the maintenance phase of the clinical trial with liraglutide. The re-submission incorporated an additional benefit from the "demonstrably less nausea" in the economic evaluation.

9. Clinical Claim

The re-submission described liraglutide (1.8mg daily) as superior in terms of comparative effectiveness and equivalent in terms of comparative safety to exenatide (10µg twice daily), but with a different safety profile ("demonstrably less nausea").

The PBAC did not accept the claim of superior comparative efficacy of liraglutide to exenatide based solely on a 0.33 % difference in HbA1c. The PBAC had previously determined that the mean difference of -0.33% in HbA1c for liraglutide 1.8 mg/day compared to exenatide in study 1797 was statistically significant and marginally clinically meaningful

(July 2011) but now considered that, on balance, the difference was of uncertain clinical benefit, considering that the translation of a 0.33 % reduction in HbA1c to clinical outcomes is uncertain and also dependent on variations in the baseline HbA1c.

The re-submission claimed that liraglutide is associated with "demonstrably less nausea" than exenatide. The duration of nausea experienced by liraglutide patients was shorter than exenatide patients.

The re-submission claimed that liraglutide is associated with statistically significantly fewer minor hypoglycaemic events compared to exenatide and this difference was included in the economic model which was appropriate. However, the economic model also included a statistically significant difference in major hypoglycaemic events favouring liraglutide, which was considered inappropriate by PBAC.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

An updated modelled economic evaluation was presented, using the CORE Diabetes Model to project long-term treatment outcomes. The type of economic evaluation presented was a cost-utility analysis.

The re-submission included additional disutility values (study by *Polster et al 2010*) for two aspects of exenatide treatment:

- The increased incidence of nausea associated with exenatide treatment; and
- The differing dosing regimens of exenatide and liraglutide, as exenatide is given twice daily within 60 minutes of both breakfast and dinner whereas liraglutide is given once daily irrespective of meals.

The results of the economic evaluation produced a base case of between $15,000 - $45,000. Results of the sensitivity analyses indicated that the key drivers of the economic model were HbA1c effect, duration of treatment, and time horizon. The model was most sensitive to the HbA1c effect, with the incremental cost per QALY gained increasing to between $45,000 - $75,000 using the upper bound of the 95% confidence interval (incremental HbA1c reduction of 0.18%) but decreasing to an incremental cost per QALY of between $15,000 - $45,000 using the lower bound of the 95% confidence interval (incremental HbA1c reduction of 0.47%).

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated was estimated by the submission to be between 10,000 – 50,000 in Year 5. The estimate was considered uncertain.

The financial cost to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be between $30 – 60 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered the requested restriction and the comparator exenatide to be appropriate.

The re-submission again presented the results of study 1797 (LEAD-6) in support of the claim of superior clinical efficacy of liraglutide over exenatide. The PBAC noted that the re-submission did not present any clinical outcome data for liraglutide with respect to reduction of cardiovascular morbidity or mortality or for other diabetes related complications. The PBAC considered there is clinical uncertainty about the relationship between intensive glycaemic control and diabetes related complications, including the use of HbA1c as a surrogate for cardiovascular outcomes as noted in recent publications. The PBAC considered that the mean difference of -0.33 % in HbA1c for liraglutide 1.8 mg/day compared to exenatide in study 1797 to be of uncertain clinical benefit, considering that the translation of a 0.33 % reduction in HbA1c to clinical outcomes is considered uncertain, dependent on variations in the baseline HbA1c and that there may be drug effects not captured by HbA1c. The PBAC noted that no data were presented on the comparative efficacy of liraglutide 1.2 mg/day and exenatide. The PBAC further noted that the long term safety of liraglutide is unknown. The PBAC therefore did not accept the claim of superior comparative efficacy of liraglutide to exenatide based solely on a 0.33 % difference in HbA1c.

The PBAC noted that the key difference in the re-submission from the July 2011 minor submission was the inclusion of additional disutilities for two aspects of treatment with exenatide. The first of these is the addition of a disutility for nausea associated with exenatide based on the submission's claim of demonstrably less nausea associated with liraglutide. The PBAC noted that this claim was based on the longer duration of nausea in the exenatide arm compared to the liraglutide arm. However, the PBAC noted that the proportion of patients reporting nausea in study 1797 was 28 % for exenatide and 25.5 % for liraglutide. The PBAC did not accept the claim of less nausea associated with liraglutide based on the data presented and considered the inclusion of the additional disutility for treatment with exenatide to be inappropriate, as the PBAC considered that patients experiencing persistent nausea will stop treatment and switch to another treatment. The second additional disutility included in the economic model attributed to treatment with exenatide was the different dosing regimen for exenatide (twice daily) and liraglutide (once daily), which the PBAC noted significantly reduced the ICER per QALY gained. The PBAC further noted that the model did not take into account other adverse effects that were not in favour of liraglutide, such as dyspepsia and constipation, nor the higher incidence of serious adverse events. The PBAC considered that the validity of the disutilities derived from Polster et al (2010) was questionable.

The PBAC noted that the re-submission claimed that liraglutide is associated with statistically significantly fewer minor hypoglycaemic events compared to exenatide. However, the economic model included a statistically significant difference in both minor and major hypoglycaemic events favouring liraglutide. The PBAC noted that the difference in major hypoglycaemic events was based on the event rate in study 1797 of nil in 235 patients for the liraglutide arm and 2 in 232 patients in the exenatide arm. The PBAC considered that this evidence to be an insufficient basis to support the claimed difference in major hypoglycaemic events.

The PBAC considered that the treatment duration applied in the economic model continued to be a source of uncertainty. As in the July 2011 submission, the re-submission assumed

that all patients treated with liraglutide switch to insulin after a defined time period. The PBAC considered that a switch to insulin after a defined time period may not reflect clinical practice and considered that the re-submission did not sufficiently address this issue.

The PBAC also noted that the clinical uncertainties associated with using incremental reduction of HbA1c as a surrogate for clinical outcomes resulted in additional uncertainty in the economic evaluation.

The PBAC considered the utilisation estimates in the re-submission to be highly uncertain, in particular the assumption of that all patients will titrate up to 1.8 mg per day of liraglutide.

The PBAC therefore rejected the submission on the basis that the claim of superior comparative effectiveness over exenatide was not accepted and on the basis of highly uncertain cost effectiveness.

The PBAC acknowledged and noted the consumer comments on this item, noting that all correspondence received was from health professionals and organisations.

Recommendation:
Reject

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 does not agree with the PBAC determination regarding the clinical uncertainty about the relationship between glycaemic control and diabetes related complications and maintains that an improvement in HbA_{1c} is an appropriate surrogate for reduced microvascular and macrovascular diabetic complications. Novo Nordisk also argues that the 0.33% incremental improvement in HbA_{1c} with liraglutide compared with exenatide is not only statistically significant but as defined by the FDA and EMA guidelines is also clinically relevant and significant. Novo Nordisk maintains that once daily liraglutide is clinically superior to twice daily exenatide and that the uncertainties raised by the PBAC such as questions around the inclusion of disutilities for dose frequency and nausea as well as the treatment duration of the health economic modelling, have all been addressed.

Novo Nordisk is disappointed that there has been a further delay in the listing of liraglutide on the PBS. However, we are committed to working with all stakeholders to find a way forward in order to make liraglutide available for people with type 2 diabetes in Australia.

Please refer to Novo Nordisk website for further information.