

## **7.13 LIRAGLUTIDE**

**injection, 3 mL pre-filled, multi-dose, disposable pen,  
6 mg/mL; 2 pen pack**

**Victoza<sup>®</sup>, Novo Nordisk Pharmaceuticals**

### **1 Purpose of Application**

- 1.1 The minor submission sought additional advice from the PBAC in relation to its March 2013 recommendation to list 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 in patients with type 2 diabetes on a cost-minimisation basis with exenatide.
- 1.2 The current minor submission requests PBAC to provide advice as to whether liraglutide 1.2 mg meets the first two criteria for a Special Pricing Arrangement (SPA) under which the published price for liraglutide will be higher than the price of its comparator, exenatide, as follows:
  1. The medicine treats a significant medical condition, and the Pharmaceutical Benefits Advisory Committee (PBAC) advises that it generates substantial incremental benefit for the intended patient population;
  2. The PBAC advises that the medicine has unique characteristics compared to any available alternative therapies or the medicine is recommended for listing in comparison with a medicine which has a similar arrangement.  
(<http://www.pbs.gov.au/industry/listing/elements/deeds-agreement/Special-Pricing-Arrangement-criteria.pdf>).
- 1.3 The submission seeks this advice on the basis of the claim that liraglutide offers additional cardiovascular benefits over exenatide. The sponsor accepts the PBAC's previous recommendation for cost-minimisation to exenatide at the effective price.

### **2 Requested listing**

- 2.1 No changes to the restriction recommended by the PBAC, which is the same as the comparator exenatide, were proposed in the submission.

### **3 Background**

- 3.1 Liraglutide has been considered by the PBAC for use in T2DM on six previous occasions (November 2010, July 2011, November 2011, March 2013, November 2015, July 2017). Liraglutide 1.2 mg once daily was recommended for listing on a cost-minimisation basis to exenatide 10 µg twice daily in dual combination therapy

with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea at the March 2013 meeting.

- 3.2 At its July 2017 meeting the PBAC did not recommend the listing of liraglutide 1.2mg and 1.8mg once daily for patients with T2DM at high risk of cardiovascular disease on the basis of inadequate comparative clinical data and uncertain cost-effectiveness. However, the PBAC reaffirmed its March 2013 recommendation to list liraglutide 1.2 mg once daily on a cost-minimisation basis with exenatide 10 µg twice daily.
- 3.3 Since the previous submission, the TGA delegate has approved a new indication for liraglutide: “in patients where Victoza is indicated to improve glycaemic control, Victoza is indicated to reduce the risk of cardiovascular events in those at high cardiovascular risk, as an adjunct to standard of care therapy”.
- 3.4 In making their decision, the TGA delegate noted that “although the ACM overall were supportive of a cardiovascular protection indication, this opinion was not unanimous. There were concerns among the group that the risk benefit and number needed to treat (NNT) was small, that we should not base a decision on a single pivotal study, that the magnitude of benefit was small, and that to approve a CV protection indication would result in marketing of this medicine to patients where this medicine would not be otherwise indicated for improvement in glycaemic control. I share the concern in relation to a single pivotal study, particularly when there is inconsistent data in relation to a class effect. However the CHMP guidelines for CV protection state that this is acceptable provided the pivotal study is large and well conducted. The LEADER study would fulfil these criteria”.

*For more detail on PBAC’s view, see section 7 PBAC advice.*

## **4 Clinical place for the proposed therapy**

- 4.1 The PBAC has previously accepted that liraglutide would offer an alternative to exenatide within the current clinical management algorithm.

## **5 Comparator**

- 5.1 The PBAC previously recommended exenatide 10 µg twice daily as the main comparator.

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item as it was a minor submission.

### **Consumer comments**

6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

6.3 As a minor submission, no new clinical trials were presented in the submission.

### **Clinical evidence**

6.4 The basis of the minor submission's request was the inclusion of prevention of CV events in the TGA registered indication for liraglutide. The data from the LEADER trial was used to support the TGA registration.

6.5 The July 2017 submission presented trial results from the LEADER trial, a long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events compared to standard of care plus placebo (NCT01179048).

6.6 The PBAC recalled that it previously noted that the dose of liraglutide in the LEADER trial was titrated to 1.8 mg, with 84.8% of patients exposed to 1.8 mg. The PBAC has only recommended listing of the 1.2 mg dose of liraglutide. The submission did not provide any evidence that the CV benefits observed in patients titrating to 1.8 mg would also be observed in patients taking 1.2 mg of liraglutide. The Pre-PBAC response stated it is reasonable to assert that the CV risk reduction in the LEADER trial is associated with the liraglutide molecule per se and is independent of the dose. However, the PBAC considered that insufficient clinical evidence was presented to support the use of liraglutide 1.2mg once daily in reducing cardiovascular risk in patients with T2DM.

6.7 The July 2017 submission nominated exenatide as the main comparator. However, clinical trial data relevant to exenatide was not provided and the submission used placebo as a proxy for exenatide treatment effects in the clinical comparison and the economic analysis. This assumed that exenatide provided no difference in reduction in cardiovascular risk for patients with Type 2 diabetes compared to placebo.

6.8 In July 2017 the PBAC accepted the evidence presented from the LEADER trial showed liraglutide had a reduction in major adverse cardiovascular events (MACE) composite outcomes (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) compared with placebo. However, it was not satisfied that liraglutide showed superior comparative effectiveness over exenatide based on the submission's assumption that the placebo arm of the LEADER trial was reasonable proxy for exenatide. The PBAC considered in the absence of clinical trial data that demonstrates exenatide has no cardiovascular effect it is likely there is a class effect across the GLP-1 analogues.

6.9 The current submission stated the EXSCEL study has shown that exenatide does not reduce the cardiovascular risk in a similar T2DM population as was used in the

LEADER trial. However, the PBAC has previously stated that an indirect comparison of liraglutide and exenatide including full evaluation of the EXSCEL trial patient characteristics and trial results was required to quantify how the CV benefits of liraglutide compare to exenatide (July 2017, PSD paragraph 7.7).

- 6.10 The submission claimed that liraglutide 1.2 mg once-daily is superior compared with exenatide 10 µg twice-daily in terms of reduced MACE.
- 6.11 The submission noted the price advantage for exenatide 2mg once weekly (Bydureon®) on the basis of potential health benefits from likely improved adherence (July 2015, PSD). The PBAC agreed there was a potential advantage for exenatide once weekly versus exenatide twice daily, but the PBAC has not accepted a potential advantage for liraglutide once daily versus exenatide twice daily.
- 6.12 The PBAC was requested to consider whether liraglutide 1.2mg once-daily meets the following SPA criteria;
- Criterion 1: The medicine treats a significant medical condition, and the Pharmaceutical Benefits Advisory Committee (PBAC) advises that it generates substantial incremental benefit for the intended patient population;  
  
The PBAC considered that this criterion appears to be met when considering liraglutide in comparison to placebo. Liraglutide is used to treatment diabetes and generates a benefit for people with diabetes.
  - Criterion 2: The PBAC advises that the medicine has unique characteristics compared to any available alternative therapies or the medicine is recommended for listing in comparison with a medicine which has a similar arrangement.  
  
The PBAC considered that this criterion was not met. Exenatide b.d. does not have a special pricing arrangement. Based on the evidence presented, the PBAC considered that liraglutide 1.2 mg has not been shown to have unique characteristics compared to exenatide b.d.

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

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

- 6.13 The submission did not provide updated financial estimates as there is no change to the proposed effective price.

## **7 PBAC Advice**

- 7.1 The PBAC advised the Minister that in its view liraglutide 1.2 mg does not meet criteria 1 and 2 for a special pricing agreement (SPA). The PBAC considered that the submission did not provide sufficient evidence to support the claim that liraglutide 1.2mg has unique characteristics compared to any available alternative therapies, and noted that liraglutide 1.2 mg was recommended for listing in comparison with

exenatide b.d., which does not have a similar arrangement.

- 7.2 The PBAC noted the TGA approval of the new indication for liraglutide to reduce the risk of cardiovascular events in those patients at high cardiovascular risk, and that this was based on a comparison to placebo. However, the PBAC noted that in the absence of presenting exenatide clinical trial data with respect to cardiovascular outcomes, the minor submission relied on the assumption that exenatide provided no difference in reduction in cardiovascular risk for patients with Type 2 diabetes compared to placebo, which was unsupported. Therefore, the PBAC could not determine if there is a class effect across GLP-1 analogues.
- 7.3 In considering the claim that liraglutide 1.2 mg once-daily showed evidence of reduced major adverse cardiovascular events (MACE) compared with exenatide 10 µg twice-daily, the PBAC recalled that at its July 2017 meeting it did not recommend the PBAC listing of liraglutide 1.2 mg and 1.8mg in patients with Type 2 diabetes mellitus and high cardiovascular risk on the basis of inadequate comparative clinical data and uncertain cost effectiveness. The PBAC considered an indirect comparison of liraglutide and exenatide including full evaluation of the EXSCEL trial patient characteristics and trial results was required to quantify how the CV benefits of liraglutide compare to exenatide. The PBAC noted that this comparison was not presented, and therefore insufficient data were presented to support the claim.
- 7.4 The PBAC noted the arguments presented in the pre-PBAC response that the claim that cardiovascular benefit of liraglutide is associated with both the 1.2 mg and 1.8 mg dose. However, the PBAC considered that this did not change its view that insufficient evidence was presented to support the use of liraglutide 1.2 mg in reducing cardiovascular risk in patients with Type 2 diabetes mellitus.
- 7.5 In the context of the SPA criteria, the PBAC reiterated exenatide twice daily does not have a special pricing arrangement, therefore in the Committee's view liraglutide once daily would not meet this criterion for an SPA.
- 7.6 The PBAC considered that should the sponsor wish to pursue a price advantage of liraglutide 1.2 mg once-daily over exenatide twice-daily, a major resubmission would be required, which would need to include an indirect comparison between liraglutide 1.2 mg and exenatide, with a full evaluation of the EXSCEL trial data, and updated economic modelling.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

The sponsor had no comment.