**PUBLIC SUMMARY DOCUMENT**
**Product:** Insulin detemir, cartridge 3mL, prefilled device 3 mL, prefilled syringe 3 mL, 100 U/mL, Levemir®
**Sponsor:** Novo Nordisk Pharmaceuticals Pty Ltd
**Date of PBAC Consideration:** November 2007

## 1. Purpose of Application
The submission sought to extend the current listing to include people with type 2 diabetes who are not responsive to oral hypoglycaemic drugs.

## 2. Background
Insulin detemir was initially considered for listing on the Pharmaceutical Benefits Scheme (PBS) in July 2005 and subsequently recommended for listing in May 2006. In the absence of sufficient evidence to support listing in type 2 diabetes, the PBAC recommended the listing of insulin detemir as a restricted benefit for type 1 diabetes on a cost minimisation basis compared with insulin glargine. *(Also see Public Summary Document for March 2006)*

## 3. Registration Status
Insulin detemir (rys) was TGA registered on the 8 June 2004 for the treatment of diabetes mellitus where used as basal insulin in combination with meal-related short- or rapid-acting insulin. Not recommended for diabetes mellitus type 2 patients who still respond to oral hypoglycaemic agents. Use in type 2 diabetes is not precluded by the registered indication.

## 4. Listing Requested and PBAC's View
The submission requested an unrestricted benefit listing.

*For PBAC's view of the requested restriction, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy
Insulin detemir is a soluble, basal insulin analogue with a prolonged duration of effect. It would provide an alternative therapy for type 2 diabetic patients who are not responsive to oral hypoglycaemic drugs.

## 6. Comparator
The submission nominated insulin glargine as the main comparator. The PBAC accepted this was appropriate.

## 7. Clinical Trials
New trial data were presented in the submission as key evidence, and comprised three direct randomised trials (Study 1373, Study 1431 and Study 2175) comparing insulin detemir (once or twice daily dosage) with insulin glargine (once daily dosage), in terms of change in HbA1c; change in fasting plasma glucose (FPG); change in weight; and relative rates of hypoglycaemic events and other adverse events.

Supplementary data not presented in previous submissions were four direct randomised trials comparing detemir and insulin NPH. Also included were two direct randomised trials and the pre- and post-treatment PREDICTIVE trial, which were presented in previous submissions.

The key trials had been not been published at the time of submission.

## 8. Results of Trials

The pooled adjusted mean difference of the reduction of HbA1c for insulin detemir compared with insulin glargine was less than 0.4% (the definition of non-inferiority).

The change in fasting plasma glucose was similar between insulin detemir and insulin glargine, and weight gain was less with insulin detemir - pooled adjusted mean difference -1.09 kg (95%CI: -1.57, -0.62).

The pooled estimates suggested no statistically significant differences in hypoglycaemic events between insulin detemir and insulin glargine (relative risks: major events 1.03 (95%CI 0.46, 2.31); nocturnal events 1.06 (95%CI 0.83, 1.36); all events 0.93 (95%CI 0.77, 1.13).

The submission presented new toxicity data from the three direct randomised trials. The rates of all adverse events were comparable between insulin detemir and insulin glargine. However, the rate of adverse events leading to discontinuation was higher with insulin detemir, as was the rate of application site disorders, although the absolute number of these events in both arms was low.

## 9. Clinical Claim

The submission claimed that insulin detemir was non-inferior to insulin glargine in type 2 diabetics.

*For PBAC's view of this claim, see Recommendation and Reasons.*

## 10. Economic Analysis

The submission presented a cost-minimisation analysis claiming that one unit of insulin detemir is equivalent to one unit of insulin glargine, based on the direct randomised controlled data. However, the PBAC had doubts regarding the equi-effective dose of detemir versus glargine.

*See Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The likely number of patients treated in year 5 was estimated to be in the range 10,000 – 50,000.

The financial cost per year to the PBS was estimated to be less than $10 million in year 5.

## 12. Recommendation and Reasons

The PBAC recommended changing the current restricted benefit listing of insulin detemir for type 1 diabetes to an unrestricted listing on a cost-minimisation basis compared with insulin glargine. The listing will now enable people with type 2 diabetes who are not responsive to oral hypoglycaemic drugs access to PBS subsidised insulin detemir.

However, the PBAC had doubts regarding the equi-effective dose of detemir versus glargine. The submission claimed that one unit of detemir was equivalent to one unit of glargine, based on the direct randomised controlled data. When the calculations were adjusted to allow for the disparate dosing of detemir and glargine in the clinical trials, the analysis suggested a

daily per unit ratio of 1.10 of detemir to glargine. Other evidence considered by the PBAC suggested higher doses of detemir might be required relative to glargine. Consequently, the PBAC requested that the Pharmaceutical Benefits Pricing Authority re-examine the dose relativity of insulin detemir in type 1 and type 2 diabetes prior to listing on the PBS.

The PBAC considered that the submission had demonstrated that insulin detemir is non-inferior to insulin glargine in type 2 diabetics, based on the pooled estimate of the primary outcome (HbA1c). The PBAC noted that weight gain is reduced with detemir, however, the rate of adverse events leading to discontinuation was higher with detemir, as was the rate of application site disorders, although the absolute number of these events in both arms was low.

***Recommendation***

Amend the restriction as follows:

Restriction: Unrestricted

Maximum quantity: 5
Repeats: 1

## 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

The sponsor is pleased that the PBAC has agreed to recommend extending the current listing for Levemir (insulin detemir) and has recommended an unrestricted listing.