Public Summary Document

Product:	Insulin detemir (rys) cartridge 3mL (Penfill®), prefilled device 3 mL, (FlexPen®), 100 U/mL, Levemir®
Sponsor:	Novo Nordisk Pharmaceuticals Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The application requested listing of insulin detemir on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit for patients who meet certain criteria, on a cost-effectiveness basis compared to insulin NPH (insulin isophane).

2. Background

This was the second listing application for insulin detemir on the PBS. The first, considered at the July 2005 meeting of the Pharmaceutical Benefits Advisory Committee (PBAC), was deferred in the absence of the sponsor's precondition for listing, namely a recommendation to list insulin glargine.

A stakeholder meeting was held in October 2005 to discuss ways forward towards possible listings of the basal insulins (detemir and glargine) on the PBS. The attendees included representatives of PBAC, clinicians, diabetes organisations, the sponsors and Government. A stakeholder meeting is non-binding on any party and is conducted without prejudice.

3. Registration Status

The Therapeutic Goods Administration (TGA) approved indication for insulin detemir (rys) is "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."

4. Listing Requested and PBAC's View

Restricted Benefit

Treatment of Type 1 or Type 2 diabetes patients requiring intensive insulin therapy with 3 or more injections of insulin per day with one of the insulins being a short acting insulin.
Type 1 or Type 2 patients with a documented protamine allergy.

The PBAC's view was that, whilst acknowledging that Type 2 diabetes patients needing multiple injections of insulin per day represented a needy population, insufficient evidence was presented to support listing in this group.

5. Clinical Place for the Proposed Therapy

The management of insulin dependent diabetes in some patients can be complicated by the trade-off between achieving better glycaemic control, as measured by a reduction in HbA1c levels, and a greater risk of hypoglycaemia resulting from a temporary relative oversupply of insulin seen with existing intermediate acting insulins. The Australian approved Product Information states that insulin detemir is a soluble, basal insulin analogue with a prolonged duration of effect.

6. Comparator

The submission nominated NPH insulin as the comparator and also presented an indirect comparison with insulin glargine, using NPH insulin as the common reference.

7. Clinical Trials

The submission provided a comparison of insulin detemir with insulin NPH (6 randomised controlled studies: five in Type 1 diabetes and one in Type 2 diabetes). The submission provided an indirect comparison of insulin detemir with insulin glargine using insulin NPH as the common comparator (9 studies comparing insulin glargine with insulin NPH are included: eight in Type 1 diabetes and one in Type 2 diabetes). The submission presented meta-analyses for each comparison.

Thirteen of the 15 studies had been published at the time of submission, as follows:

Trial/first author	Protocol/Publication title	Publication citation
NN304-1335/ Russell-Jones D	A Six Month, Multi-centre, Open-label, Parallel Efficacy and Safety Comparison of Insulin detemir and NPH insulin in Patients with Type 1 Diabetes on a Basal-bolus Regimen.	Clinical Therapeutics, 2004 26(5):724-736.
NN304-1448/ Home P	A 16 week, multi-centre, multi-national, open, randomised three-group parallel study comparing administration of insulin detemir at 12 hour intervals, insulin detemir morning and bedtime and NPH morning and bedtime in patients with Type 1 diabetes: A Phase III Trial	Diabetes Care, 2004, 27(5):1081-1087
NN304-1336/ Haak T	A Six-Month, Multi-centre, Open, Asymmetrically Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Patients with Type 2 Diabetes on a Basal - Bolus Regimen.	Diabetes Obesity & Metabolism 2005; 7:56-65.
NN304-1447/ Pieber TR	Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin.	Diabetic Medicine 2005; 22(7):850-7
Rosenstock J	Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens.	Diabetes Care, 2000, 23(8):1137-1142.
Hershon K	2004. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes.	1.Endocrine Practice, 2004, 10(1):10-17. 2.Diabetiologia, 2001,44:52. 3.Diabetes, 2001,50(Suppl 2):A116-A117.
Rossetti P	Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime.	Diabetes Care, 2003, 26(5):1490-6.
1. Schober E 2. Van Dyke J 3. Schober E	Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus.	1.J Pediatric Endocrinology & Metabolism, 2002, 15(4):369-76. 2.J Pediatric Endocrinology & Metabolism, 2000, 13(Suppl):34. 3. Diabetes Care, 2001, 24(11):2005-6.
Raskin P	A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes.	Diabetes Care, 2000, 23(11):1666-71.

Trial/first author	Protocol/Publication title	Publication citation
Pieber TR	Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes.	1. Diabetes Care, 2000, 23(2):157-62. 2. Diabetes, 1998, 47:242. 3. Diabetiologia, 1998, 41:187
1. Ratner RE 2-3. Garg SK	Less hypoglycaemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes.	1. Diabetes Care, 2000, 23(5):639-43. 2. Diabetes, 2001, 50:A435-6. 3. Diabetes, 1998, 47:1390
Porcellati F	Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin.	1. Diabetic Medicine, 2004, 21(11):1213-1220. 2. Diabetes, 2002, 51(Suppl 2):A53.
1. Rosenstock J 2- 4. Fonseca V	Less symptomatic hypoglycaemia with bedtime insulin glargine (LANTUS) compared to bedtime NPH insulin in patients with type 2 diabetes.	1. Diabetes Care, 2000, 23(8):1137-1142. 2. Diabetes, 2001, 5O (Suppl 2):All2. 3. Diabetologia, 2001, 44:796. 4. Am J of Med Sci 2004; 328(5): 247 – 80

* The Hershon et al (2004) glargine trial is a sub-set of the Ratner et al (2000) trial, including only patients on once-daily glargine or twice-daily NPH.

The submission also presented data from an observational study as supportive evidence. This was a global, multicentre, open label, nonrandomised, non-interventional, observational, safety study using insulin detemir for the treatment of insulin requiring Type 1 or Type 2 diabetes mellitus sponsored by Novo Nordisk. This study had not been published at the time of submission.

8. Results of Trials

For the primary efficacy variable, HbA1c, the submission's meta-analyses of selected trials demonstrated that insulin detemir is no worse than insulin NPH (insulin isophane) for both Type 1 and 2 patients combined and Type 1 patients alone. There was a significant improvement in fasting plasma glucose levels with detemir compared with NPH for both Type 1 and 2 patients combined (-1.10mM) and Type 1 patients alone (-1.42mM). The patient cohort on insulin detemir also gained significantly less weight than those on NPH (-0.72kg for Type 1 and 2 patients combined and -0.71kg Type 1 patients alone).

There was a statistically significant advantage for insulin detemir compared to NPH in the reduction of all hypoglycaemic events and nocturnal hypoglycaemic events. There was a difference between detemir and NPH in the occurrence of major hypoglycaemic events (major hypoglycaemic events being those in which the subject requires assistance from a third party), however this difference did not reach statistical significance. The reduction in number of events was small.

In the trial in intensively treated Type 2 diabetes (1336), (the target population recommended by the participants at the stakeholder meeting and therefore the Type 2 population targeted by the sponsor's proposed restriction), no significant differences were found between insulin detemir and NPH in end of treatment HbA1c, baseline and end of treatment FPG (mmol/L), and the percentages of all, nocturnal and major hypoglycaemic events (major hypoglycaemic events being those in which the subject requires assistance from an outside source). The patient cohort on insulin detemir gained significantly less weight than those on NPH (mean difference 0.8 kg).

The indirect comparison between insulin detemir and insulin glargine showed that there was no statistically significant difference for change in HbA1c, FPG and weight, and reductions in hypoglycaemic events, for Type 1 and 2 patients combined and Type 1 patients alone.

For PBAC's view of these results, see Recommendations and Reasons

9. Clinical Claim

The submission claimed that insulin detemir:

- had significant advantages in effectiveness and less toxicity than insulin NPH, and
- was no worse than insulin glargine in terms of effectiveness and toxicity.

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

10. Economic Analysis

The submission provided a preliminary economic evaluation employing a cost-effectiveness analysis using NPH insulin as a comparator. The PBAC had some concerns with the assumptions underlying this analysis and considered there was uncertainty in the resulting incremental cost effectiveness ratios (ICERs).

The submission also presented a cost-utility analysis with NPH as comparator based on utility gained from a reduction in hypoglycaemic events and utility gained from reduction in fear of hypoglycaemic events (utility values literature-based, event rates literature-based, event rate reductions trial-based; second analysis using event rates and reductions in the observational study). The base case modelled incremental cost/extra quality adjusted life year (QALY) gained ranged within $45,000 - $75,000 to < $15,000, as the re-submission presented a range of base case utility values. The incremental cost/extra QALY gained based on the observational study was < $15,000. *For PBAC's view of these results, see Recommendations and Reasons.*

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients treated with insulin detemir through the PBS to be within the range of 100,000 – 200,000 per year in Year 4. The submission assumed that the number of patients/year would not change if insulin glargine was also PBS-listed.

The additional cost to the PBS was estimated to be approximately $30 – 60 million per year in Year 4. These calculations did not take into account a possible PBS listing for insulin glargine. However, as the submission expected the cost to the Commonwealth for insulin glargine and insulin detemir to be the same, the budget impact would be the same.

12. Recommendation and Reasons

The PBAC again acknowledged the clinical need for an insulin product that reduces hypoglycaemic events without compromising long-term diabetic control as measured using HbA1c. The Committee expressed sympathy with those patients and clinicians who report benefit from treatment with long-acting basal insulins, but continued to have difficulty reconciling these individual clinical experiences with the body of randomised trial evidence provided in the sponsors' submissions.

The Committee agreed that for the efficacy variable, change in HbA1c, the submission's meta-analyses of selected trials demonstrated that insulin detemir is no worse than insulin NPH (insulin isophane) for both Type 1 and 2 patients combined and Type 1 patients alone.

The PBAC noted that the submission includes only one trial in Type 2 diabetes (1336). No significant differences were found between insulin detemir and NPH in end of treatment HbA1c, baseline and end of treatment FPG (mmol/L), and the percentages of all, nocturnal and major hypoglycaemic events (major hypoglycaemic events being those in which the subject requires assistance from an outside source).

Additionally, two publications of insulin detemir trials in Type 2 diabetes located in the literature, and included in the submission, did not report superior efficacy or reduced hypoglycaemia for insulin detemir.

The Committee further noted that there were three randomised trials comparing detemir with NPH presented to the Therapeutic Goods Administration (TGA). Two of the three trials (1337: combination therapy with metformin and 1166: insulin detemir monotherapy), using a non-marketed formulation with a lower insulin concentration, showed inferior glycaemic control at 6 months, as reflected in the TGA approved product information. The submission to the PBAC excluded these two trials, but the PBAC found the reasons for their exclusion to be unconvincing, even in the context that the submission does not request listing of insulin detemir for these patients. The TGA-approved indication refers to the clinical trials section when recommending that insulin detemir not be used in Type 2 patients who still respond to oral hypoglycaemic agents.

The PBAC therefore decided that the application seeking listing for insulin detemir in Type 2 diabetics, albeit in the sub-set of Type 2 diabetes requiring 3 or more injections of insulin per day, should be rejected. The Committee acknowledged that Type 2 diabetes patients need multiple injections of insulin per day represented a needy population, but insufficient evidence was presented to support listing in this group.

With respect to Type 1 diabetes, the PBAC agreed the evidence presented showed there are statistically significant reductions for insulin detemir over NPH in the rates of all hypoglycaemic events and nocturnal hypoglycaemic events, but no significant difference in the rate of major hypoglycaemic events. The estimated reduction in number of hypoglycaemic events was small and the PBAC was uncertain whether these reductions were clinically important. Further, the measure of events avoided per patient per year does not provide information about the distribution of changes in event rates across patients, particularly whether some patients experience large and perceptible changes in event rates, while others experience imperceptible changes.

The PBAC noted that there was uncertainty surrounding the impact of these reductions for the average patients. If the average change in rates does not have an important impact on the average patient, then this raises substantial doubt regarding the assumption for the modelled economic evaluation that, on average, there will be a utility gain associated with a reduction in the fear of subsequent hypoglycaemic events. Such a utility gain may only arise in the small sub-set of patients with a directly perceptible reduction in event rates, in which case the claimed utility gain from reduced fear should only apply to this sub-set.

The Committee noted that the indirect comparison provided in the submission showed that there was no statistically significant difference between insulin detemir and insulin glargine for change in HbA1c, FPG and weight, and reductions in hypoglycaemic events, for Type I and II patients combined and Type I patients alone. Although recognising that the results of this indirect comparison should be interpreted with caution, the Committee was reassured by results of this comparison.

The PBAC considered that, for a number of reasons, the non-randomised "before and after" observational study did not provide additional relevant clinical information over the evidence provided by the randomised controlled trials. The Committee thus further considered that it was inappropriate to rely upon the incremental cost-effectiveness ratios (ICERs) generated during the modelled economic evaluation using the results from the observational study, and that the more appropriate ICERs were those generated using the results from the randomised controlled trials.

The Juvenile Diabetes Research Foundation (JDRF) Survey results, tabled at the meeting, were based upon 302 responses obtained from an on-line survey of 1000 randomly chosen members of JDRF with a connection with Type 1 diabetes, and for whom on-line address details were available. As such the population was likely to be biased, and the Committee felt unable to draw any conclusions from the results although it commended JDRF for attempting this work.

The Committee had a number of concerns with the submission's modelled economic analysis. It further considered that the modelled ICERs generated using the trial-based results were unacceptably high and uncertain.

Overall, taking into account the uncertainty over the clinical importance of the reduction in hypoglycaemic events in Type 1 diabetes, together with doubts about the economic model and the resulting high and uncertain cost effectiveness ratios, the PBAC did not consider that the price advantage requested over insulin NPH in the submission was justified, even if a PBS listing were to be restricted to Type 1 patients alone.

The Committee however recalled that insulin analogues were recommended for listing as unrestricted benefits on a cost effectiveness basis over neutral insulin on the grounds of an improvement in the rate of hypoglycaemic events. Taking this into account, the PBAC indicated that a listing of insulin detemir could follow the same logic.

The Committee consequently deferred this item, indicated that, should the sponsor formally indicate an acceptable basis for a cost-effectiveness recommendation, the PBAC would be prepared to reconsider this matter out-of-session.

Further information

Following a response from the sponsor, further consideration by the PBAC occurred at an extraordinary meeting held on 3 May 2006. 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.

The PBAC noted that the indirect comparison provided in the submission (which included five trials in Type 1 and one in Type 2 diabetes) showed that there was no statistically significant difference between insulin detemir and insulin glargine for change in HbA1c, FPG and weight, and reductions in hypoglycaemic events, for Type 1 and 2 patients combined and Type 1 patients alone.

The PBAC confirmed its earlier conclusions with respect to the use of insulin detemir in Type 2 diabetes patients, and decided that based on the evidence submitted use on the PBS should be restricted to Type 1 patients only.

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 that the PBAC's recommendation provided a baseline platform for further dialogue for the listing of insulin detemir. After considerable negotiation between both parties, an agreement has been reached which has ultimately allowed insulin detemir to progress towards a listing for all type 1 diabetes.

Novo Nordisk looks forward to basal insulin analogues being made available for the people who need it most – the type 1 diabetes population.