

PUBLIC SUMMARY DOCUMENT

Product: Insulin degludec, injection solution, 100 IU/mL and 200 IU/mL, Tresiba Flextouch® and Tresiba Penfill®

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested an unrestricted listing for use in the treatment of patients with type 1 or 2 diabetes mellitus.

2. Background

This product had not previously been considered by the PBAC.

3. Registration Status

TGA status at time of PBAC consideration: The submission was considered under the TGA/PBAC parallel process. At the time of PBAC consideration, only the Clinical Evaluation Report was available.

Insulin degludec was TGA registered in November 2017 to improve glycaemic control in adult patients with diabetes mellitus requiring insulin.

4. Listing Requested and PBAC's View

The submission requested an unrestricted Section 85 listing.

5. Clinical Place for the Proposed Therapy

Insulin degludec is an ultra-long acting basal insulin to be used in combination with short and/or rapid acting insulin in patients with type 1 diabetes and in combination with oral anti-diabetic medication and/or rapid acting insulin in patients with type 2. Insulin degludec was proposed as a replacement therapy for other basal insulin's: glargine, detemir and isophane in type 1 patients and glargine and isophane in type 2 patients.

While the submission did not clearly describe the proposed treatment algorithm for type 1 diabetes, the PBAC considered it was likely to be used in patients transferring from other basal insulins, in combination with bolus insulin. In type 2 diabetes, the product was anticipated to be used alongside currently listed insulins and after metformin and/or a sulfonylurea.

6. Comparator

The submission nominated insulin glargine as the main comparator as this is the most commonly used basal insulin. The PBAC considered that this was reasonable.

7. Clinical Trials

The submission presented seven head-to-head randomised trials comparing insulin degludec and insulin glargine: NN1250-3583 and NN1250-3770 (Type 1 basal bolus), NN1250-3579, NN1250-3672, NN1250-3586 and NN1250-3668 (Type 2 basal oral) and NN1250-3582 (Type 2 basal bolus plus orals).

Details are presented in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Trial NN1250-3583 Heller et al.	Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial	<i>The Lancet</i> ; 2012, 379(9825): 1489-1497
Trial NN1250-3770	A 26-week trial investigating the dosing flexibility, efficacy and safety of NN1250 in subjects with type 1 Diabetes with a 26-week extension.	Clinical trials.gov ID: NCT01079234
Trial NN1250-3582 Garber et al	Insulin degludec versus insulin glargine in basal-bolus therapy with mealtime insulin aspart in type 2 diabetes: a 52-week, phase 3, randomised, parallel-group, multinational, treat-to-target trial (BEGIN™ BB T2)	<i>Lancet</i> 2012; 379, (9825): 1498 - 1507
Trial NN1250-3579 Zinman et al.	Insulin Degludec versus insulin glargine in insulin-naïve patients with type 2. A 1-year, randomized, treat-to-target trial (BEGIN™ Once Long)	<i>Diabetes Care</i> 2012 Vol: In press
Trial NN1250-3586	A Pan-Asian Trial comparing efficacy and safety of NN1250 and insulin glargine as add on to OAD(s) in subjects with type 2 diabetes (BEGIN™: ONCE ASIA)	Clinical Trials.gov ID: NCT01059799
Trial NN1250-3668	A 26-week Randomised, Controlled, open-label, Multi-centre, multi-national three-arm treat-to-target comparing efficacy and safety of three different dosing regimens of either NN1250 or Insulin glargine with or without combination with OAD treatment, in subjects with type 2 Diabetes Mellitus (BEGIN™ FLEX)	Clinical Trials.gov ID:NCT01006291
Trial NN1250-3672	Comparison of NN1250 with insulin glargine in patients with type 2 Diabetes (BEGIN™)	Clinical Trials.gov ID:NCT01068665

8. Results of Trials

The clinically relevant outcomes for benefits and harms were change in HbA1c and occurrence of hypoglycaemia.

The results for change from baseline in HbA1c from the published trials (3583, 3582 and 3579) are presented in the table below.

Change from baseline in HbA1c across the trials

Trial	Degludec			Glargine			Difference ^a (95% CI)
	Baseline Mean (SD)	Endpoint Mean (SD)	LS Mean change ^a (SE)	Baseline Mean (SD)	Endpoint Mean (SD)	LS Mean change ^a (SE)	
Type 1 basal bolus							
3583	N=472 7.7 (0.9)	7.34 (0.05)	-0.36 (0.05)	N=157 7.7 (1.0)	7.35 (0.07)	-0.34 (0.07)	-0.01 (-0.14, 0.11)

Trial	Degludec			Glargine			Difference ^a (95% CI)
	Baseline Mean (SD)	Endpoint Mean (SD)	LS Mean change ^a (SE)	Baseline Mean (SD)	Endpoint Mean (SD)	LS Mean change ^a (SE)	
Chi-square for heterogeneity: P= not provided I ² statistic with 95% uncertainty interval = not provided							
Type 2 basal oral							
3579	N=773 8.2 (0.8)	7.11 (0.04)	-1.06 (0.04)	N=257 8.2 (0.8)	7.02 (0.06)	-1.15 (0.06)	0.09 (-0.04, 0.22)
Chi-square for heterogeneity: P= not provided I ² statistic with 95% uncertainty interval = not provided							
Type 2 basal bolus plus oral							
3582	N=744 8.3 (0.8)	7.19 (0.06)	-1.10 (0.06)	N=248 8.4 (0.9)	7.11 (0.08)	-1.18 (0.08)	0.08 (-0.05, 0.21)

In all trials the non-inferiority of degludec to glargine for change in HbA1c was demonstrated, with the upper limit of the 95% CI for treatment differences less than 0.4%. The pooled analyses presented in the submission confirmed the non-inferiority of degludec and glargine.

The submission presented results for occurrence of hypoglycaemic events (a safety outcome in the trials) as a secondary efficacy outcome. The PBAC noted that the individual trial results showed few differences between insulin degludec and glargine. Insulin degludec was statistically significant for non-severe nocturnal hypoglycaemia. The PBAC noted the data suggested a small reduction in hypoglycaemia, but that it remained unclear whether this would translate into clinically meaningful benefits. In particular, the PBAC noted

- that severe hypoglycaemic events were not reduced;
- the results for change in HbA1c from baseline across the trials, indicated the point estimate of HbA1c reduction was slightly less for insulin degludec than for glargine in Type 1 basal bolus patients;
- the protocols used in the trials were a strict ‘treat to target’ design as required by the FDA and EMA regulatory authorities but that this may not be representative of clinical practice.

The submission claimed advantages for change in quality of life based on the SF-36 results derived from a pooled meta-analysis which demonstrated a trend favouring insulin degludec in all of the treatment groups. The PBAC did not consider this claim was appropriate given that significant advantages were only observed on 3 of 10 sub-components for type 2 diabetes patients on a basal oral regimen, 1 of 10 sub-components for type 2 patients on basal bolus + oral regimen and no differences for type 1 diabetes patients.

With regard to safety (other than hypoglycaemic events), the trial data suggested little difference between insulin degludec and glargine. No statistically significant difference was observed across the trials for most categories of adverse events. The PBAC noted concerns raised by the FDA about the potential for an increase in cardiovascular risk in subjects randomised to insulin degludec relative to the comparator. The PBAC noted that while two years of collected data identified no concerning safety issues, the long-term safety of insulin degludec remained unknown.

9. Clinical Claim

The submission described insulin degludec as non-inferior to glargine in terms of HbA1c control and superior in terms of comparative safety, with the latter due to a reduced risk of hypoglycaemia.

The PBAC accepted the submission's claim of non-inferior effectiveness but did not consider that the claim of superior safety was adequately supported given that it remained unclear whether the claimed reduction in hypoglycaemia will translate into clinical benefits.

10. Economic Analysis

The submission presented a stepped economic evaluation, based on direct randomised trials and using a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis. Two models were presented, the first model was a 'trial-based' model using treatment utilities for degludec, and glargine along with literature sourced disutilities for self-monitoring of blood glucose (SMBG) testing and utilities for flexible dosing. The second model was described as 'event-based', and used literature-sourced disutility values for hypoglycaemic events, along with literature-sourced disutilities for SMBG testing and utilities for flexible dosing.

The time horizon used in the modelled evaluation was 1 year, which the PBAC did not consider to be appropriate given the chronic nature of diabetes.

The base case ICERs were all less than \$10,000 per quality adjusted life year (QALY) for type 1 basal bolus, type 2 basal oral, type 2 basal bolus, all type 2 weighted and type 1 and 2 weighted.

The models were most sensitive to frequency of SMBG testing, an advantage for degludec that may not be seen in clinical practice. The PBAC did not consider that the assumption of lower SMBG use, the key driver in the model, was adequately justified.

Assuming an equivalent frequency of SMBG for degludec and glargine, the ICERs ranged from less than \$15,000 to between \$75,000 and \$105,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The estimated net cost to the PBS was between \$30-60 million in Year 5 and a total cost over the first 5 years of listing of over \$100 million.

12. Recommendation and Reasons

The PBAC noted that the submission was submitted under TGA/PBAC parallel process. The clinical evaluation report was available to the PBAC at the time of consideration.

The PBAC rejected the application to list insulin degludec on the basis that the claim of superior safety over insulin glargine was not adequately justified, and cost-effectiveness was therefore not supported. The modelling approach in the submission was not considered

appropriate by the PBAC and the results were mainly driven by potential differences in Self-Monitoring of Blood Glucose (SMBG) testing, rather than trial based differences. The ICERs generated showed a large variance in results across the type of diabetes and treatment regimen and were therefore considered unreliable.

The submission argued that insulin degludec would lead to a lower use of SMBG. This reduction is a key driver of the model results. The PBAC did not consider that this assumption was adequately justified, and considered that these differences in cost should be excluded from the economic evaluation.

Overall, the PBAC considered there were a number of issues with the model:

- Some parameters included in the model were sourced from literature which did not appear to be applicable to the proposed PBS population;
- The use of a one year time horizon was not considered appropriate for a chronic disease. The SF-36 results from the trial were mapped to the EQ-5D for modelling. The PBAC agreed with the ESC that it would have been more appropriate to base utilities on the SF-6D algorithm rather than a mapping approach; and
- Differences in quality of life assumed in the model were not considered adequately supported by the trial results.

The PBAC considered that the results of the model were highly uncertain, given the issues noted above. The PBAC was also concerned about the potential cardiovascular risks associated with insulin degludec, in the absence of any TGA advice on this issue.

The PBAC considered that any re-submission should be a major submission. Based on the information available in the submission, a cost minimisation approach against glargine may be more appropriate. However, if a cost effectiveness claim is presented, the PBAC considered that any re-submission should address the issues raised about the duration of the model, the derivation of the utilities applied and the applicability of costs from literature to the proposed population.

The PBAC noted that the submission is eligible for an Independent Review.

Recommendation:

Rejected

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 of the hypoglycaemia benefit of insulin degludec, and believes that any reduction in hypoglycaemia is of significant importance to the actual patient who experiences these events. Novo Nordisk is disappointed with the PBAC's recommendation but will continue to

work constructively with the PBAC to ensure that insulin degludec is made available for patients and physicians dealing with the burden of diabetes as soon as possible.