7.02 INSULIN DEGLUDEC, Solution for injection 100 units per mL, Tresiba® Penfill®, Novo Nordisk Pharmaceuticals Pty. Ltd.

1 Purpose of submission

1.1 The standard re-entry submission requested a General Schedule Restricted Benefit listing for insulin degludec 100 IU/mL for the treatment of type 1 diabetes mellitus (T1D).

1.2 The listing was requested on the basis of a cost consequences analysis compared to insulin glargine 100 IU/mL.

1.3 The Pre-Sub-Committee Response (PSCR) stated that the rationale for the resubmission was to address a small but important patient and clinician need, which the sponsor was advised by "local clinical experts" will arise because of the pending discontinuation of insulin detemir from the Australian market towards the end of 2026. While the PSCR stated that PBS listing of insulin degludec is only "possible (or indeed necessary) if the PBAC agrees with the local expert advice … received, that for at least some T1DM patients, IDeg [insulin degludec] offers important and/or practical benefits over IGlar [insulin glargine] 100 IU/mL...", the ESC noted that the resubmission and PSCR did not state who the local experts were, just that they advised "there is an urgent need for an alternative stand-alone long-acting insulin analogue to be supplied via the PBS for treatment of patients with T1D, particularly those aged less than 6 years but also for older patients for whom Toujeo® [insulin glargine] or Ryzodeg® [insulin detemir/insulin aspart] are not clinically appropriate or optimal" (p11 of the resubmission).

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Type 1 diabetes in patients aged 1 year or older.
Intervention	Insulin degludec 100 IU/mL administered once daily by subcutaneous injection in individualised doses.
Comparator	Insulin glargine 100 IU/mL.
Outcomes	Glycaemic control; total daily insulin dose; rate of hypoglycaemia episodes, and other adverse events.
Clinical claim	Insulin degludec 100 IU/mL provides at least non-inferior effectiveness and safety compared to insulin glargine 100 IU/mL, with important clinical advantages for some patients.

Source: Table 1-1, p12 of the resubmission.

2 Background

Registration status

2.1 Insulin degludec is currently listed on the Australian Register of Therapeutic Goods (ARTG) for the "Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year". At the time of PBAC consideration, an amendment to vary the pregnancy category from Category B3 to Category A was under consideration by the TGA, and the first round TGA clinical evaluation report was available. The TGA clinical evaluator recommended approving this change.

Previous PBAC consideration

2.2 The PBAC previously considered insulin degludec for the treatment of T1D and type 2 diabetes (T2D) at its March 2013 meeting. The PBAC did not recommend insulin degludec for T1D or T2D on the basis that the claim that insulin degludec demonstrated superior safety over insulin glargine (the main comparator) was not adequately justified, and cost-effectiveness (which relied on the claim of superior safety in terms of reduced hypoglycaemia events) was therefore not supported. The PBAC considered that the claim of non-inferior effectiveness versus insulin glargine was supported in T1D and T2D (p. 3, Insulin degludec Public Summary Document [PSD], March 2013 PBAC meeting).

2.3 Compared to the March 2013 submission, the main changes in the resubmission were:

- The resubmission requested a PBS listing for insulin degludec for the treatment of T1D only.
- The resubmission proposed a special pricing arrangement (SPA) incorporating a [redacted]% rebate.
- The resubmission presented clinical evidence for T1D only, including 2 clinical studies considered at the March 2013 meeting, 3 clinical studies not previously considered by the PBAC, 2 network meta-analyses, and 11 supportive studies in selected populations and circumstances of use.
- The resubmission presented a cost consequences economic analysis, instead of a cost effectiveness analysis.
- The resubmission presented revised financial implications.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of Rpts	Available brands
General Schedule – Restricted Benefit: Type 1 diabetes					
Insulin degludec 100 IU/mL 5 x 3 mL cartridges	$400.77 (published price) $[redacted] (effective price)[a]	5	5	1	TRESIBA® Penfill®
Note: Special Pricing Arrangements apply					

[a] The method of calculating the effective dispensed price for maximum quantity (DPMQ) from the effective ex-manufacturer price in the resubmission was not based on standard methods, and did not account for the differences in fees and markups for the published and effective DPMQs.

3.1 The resubmission requested a General Schedule Restricted Benefit listing for insulin degludec 100 IU/mL (3 mL cartridges, Penfill®), for patients with T1D, appropriate for prescribing by medical practitioners and nurse practitioners.

3.2 The resubmission proposed a Special Pricing Arrangement (SPA), stating that the [redacted]% rebate would achieve an effective approved ex-manufacturer price (AEMP) of $[redacted], translating to an effective dispensed price for maximum quantity (DPMQ) of $[redacted]. The evaluation and the ESC noted that an effective AEMP of $[redacted] recalculated using standard methods equates to an effective DPMQ of $[redacted].

3.3 Table 2 compares the proposed price of insulin degludec with prices of available PBS-listed basal insulin therapies.

Table 2: Basal insulin price comparison

	PBS listing	Pack size (Max qty)	Published DPMQ	Effective DPMQ
Insulin degludec 100 IU/mL*	T1D (proposed)	5 × 3 mL (5)	$400.77	Submission: $[redacted] Evaluation: $[redacted]
Insulin detemir 100 IU/mL	T1D	5 × 3 mL (5)	$356.22	$[redacted]
Insulin glargine 100 IU/mL	Unrestricted	5 × 3 mL (5)	$187.42	No SPA
Insulin glargine 300 IU/mL	Unrestricted	5 × 1.5 mL (5)	$420.87	CIC
Insulin glargine 300 IU/mL	Unrestricted	3 × 1.5 mL (5)	$255.97	CIC
Insulin degludec 70 IU/mL + Insulin aspart 30 IU/mL	Unrestricted	5 × 3 mL (5)	$381.02	$[redacted]
Insulin aspart 100 IU/mL	Unrestricted	5 × 3 mL (5)	$167.52	No SPA

Source: Constructed during the evaluation.

Abbreviations: AEMP, approved ex-manufacturer price; CIC, Committee-In-Confidence; DPMQ, dispensed price for maximum quantity; EMP, ex-manufacturer price; IU, International Units; NA, not applicable; SPA, special pricing arrangement; T1D, type 1 diabetes.

* The effective DPMQ proposed in the resubmission of $[redacted] included markups calculated based on an EMP of $[redacted] (calculated from the published DPMQ). It was recalculated during the evaluation to $[redacted] based on the insulin degludec effective maximum quantity EMP of $[redacted].

3.4 The requested PBS indication was narrower than the TGA approved indication as it excluded patients with T2D. The resubmission acknowledged that the requested PBS indication was narrower than the TGA approved indication and the unrestricted General Benefit listing of insulin glargine 100 IU/mL (the main comparator) but argued that the restriction was appropriate given the context and intent of the proposed listing. The ESC advised there is potential risk of insulin degludec use outside the requested restriction, in patients with T2D. The PSCR stated that while insulin

degludec would also be clinically appropriate for patients with T2D that the sponsor would not be seeking a PBS listing as the same unmet need does not exist for this patient group. The PSCR stated that if this is a matter of concern, a listing subject to an Authority Required restriction would be acceptable.

3.5 The requested restriction was broader than the populations in the clinical studies presented in the submission, which excluded patients aged <18 years and women during pregnancy.

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

4 Population and disease

4.1 T1D is a lifelong autoimmune condition affecting insulin producing beta cells in the pancreas, which most commonly presents in people aged under 30 years, but can also occur later in life (AIHW, 2025). The causes of T1D are incompletely understood but may be related to environmental factors in patients with an underlying genetic disposition. In children, onset is usually abrupt and the symptoms obvious, while in adults, onset is often slower to develop and more difficult to recognise and diagnose.

4.2 The symptoms of uncontrolled T1D may include polydipsia (excessive thirst), polyuria (excessive urine production), polyphagia (excessive hunger), unexplained weight loss, weakness, fatigue, headache, dizziness, blurred vision and ketosis (Diabetes Australia, 2025). People with T1D require lifelong daily insulin replacement therapy (AIHW 2025). The key aims of T1D management are maintaining optimal glycaemic control (minimising the incidence of hypoglycaemia or hyperglycaemia), reducing the overall risk of diabetes related complications (retinopathy, nephropathy, neuropathy and cardiovascular events/disease) and optimising patient/carer health related quality of life, physical, mental and social functioning, lifestyle and daily activities.

4.3 The prevalence of T1D in Australia is estimated at around 134,000 persons, representing about 10% of all diabetes cases nationally (Diabetes Australia, 2025). However, local prevalence data are considerably more accurate and complete for persons aged less than 19 years than adult populations (AIHW, 2025).

4.4 Insulin degludec is an individually titrated, once daily ultra long-acting basal insulin analogue, supplied as a solution for injection (100 IU/mL or 200 IU/mL), administered by subcutaneous injection using a proprietary pre-filled pen or cartridge. The requested PBS listing is for insulin degludec 100 IU/mL, in 3 mL multidose cartridges (Penfill®). The insulin degludec 200 IU/mL formulation was not included in the resubmission.

4.5 Insulin degludec dosing for the treatment of T1D is individualised in accordance with patient requirements to optimise glycaemic control based on fasting plasma glucose (FPG) and must be combined with short and/or rapid acting insulin to cover mealtime insulin requirements. Insulin degludec may be administered at any time of the day,

but preferably the same time every day. Insulin degludec is not suitable for administration via insulin pump.

4.6 The sponsor stated that insulin detemir is scheduled for discontinuation in the Australian setting by the end of 2026. The resubmission claimed that insulin degludec is expected to replace insulin detemir in affected patients, given the needs of those patients for an alternative ultra-long-acting basal insulin and based on expert opinion on the need for a viable PBS-listed alternative long-acting insulin for T1D patients. The resubmission stated that most affected patients expected to switch to insulin degludec would otherwise switch to insulin glargine if insulin degludec is not listed on the PBS.

4.7 The clinical management algorithm positioned insulin degludec 100 IU/mL as an alternative to insulin glargine 100 IU/mL or insulin glargine 300 IU/mL (in patients aged 6 years and older), for the treatment of patients with T1D not using a less intensive fixed dose insulin regimen or premixed basal-bolus regimen, or an insulin pump, replacing insulin detemir after its withdrawal from the Australian market at the end of 2026.

4.8 In Australia, insulin glargine 100 IU/mL is approved for the treatment of T1D in adults and children, and T2D in adults who require insulin for the control of hyperglycaemia, and insulin glargine 300 IU/mL is approved for the treatment of diabetes mellitus in patients 6 years of age and older.

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

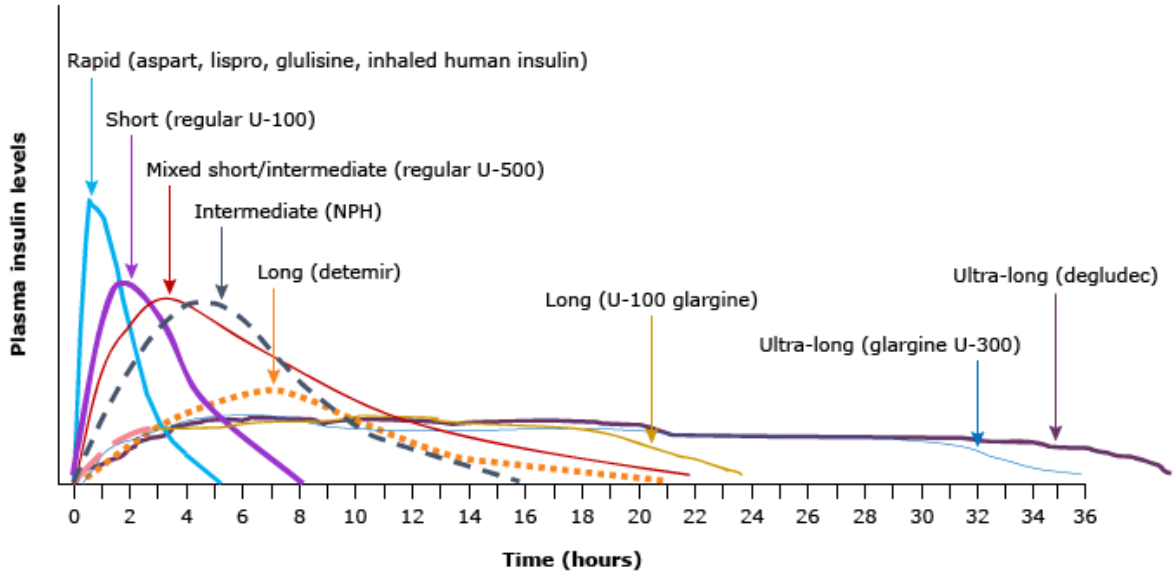
5 Comparator

5.1 The resubmission nominated insulin glargine 100 IU/mL as the main comparator. In support of this nomination the resubmission stated that if insulin detemir is delisted, most affected patients will switch to insulin degludec, if PBS-listed, but would otherwise switch to insulin glargine if insulin degludec is not reimbursed on the PBS. The ESC considered that the resubmission did not adequately justify the selection of insulin glargine 100 IU/mL over insulin glargine 300 IU/mL as the main comparator.

5.2 At the March 2013 meeting, the PBAC considered that insulin glargine 100 IU/mL (the only formulation listed on the PBS at that time) was the appropriate main comparator (p1, Insulin degludec PSD, March 2013 PBAC meeting). The evaluation noted that insulin glargine 300 IU/mL was recommended by the PBAC for the treatment of T1D and T2D at the July 2015 meeting, based on a cost-minimisation approach (CMA) with insulin glargine 100 IU/mL (para 7.1, Insulin glargine 300 IU/mL PSD, July 2015 PBAC meeting), and considered that it may also be a relevant comparator. The PSCR stated that some patients might substitute insulin degludec for insulin glargine 300 IU/mL and that it may therefore be a theoretical secondary comparator.

5.3 The ESC noted the pharmacokinetic profile of various single insulin products (Figure 1) and considered that based on its pharmacokinetic profile, that insulin degludec was most similar to insulin glargine 300 IU/mL.

Figure 1: Pharmacokinetic profile of single insulin products



Source: UpToDate, 2025

5.4 As such, the ESC considered insulin glargine 300 IU/mL to be an equally appropriate comparator given its pharmacokinetic profile and noted the two formulations are not interchangeable with the equi-effective doses being 1 unit of insulin glargine 300 IU/mL being equivalent to 0.84 units of insulin glargine 100 IU/mL (para 7.5, Insulin glargine 300 IU/mL PSD, July 2015 PBAC meeting). The ESC further noted that insulin glargine 300 IU/mL is not recommended for children aged less than 6 years, and considered that for children in this age range, insulin glargine 100 IU/mL would be the appropriate comparator.

5.5 The resubmission acknowledged that while the majority of initial use for insulin degludec is expected to be in patients currently treated with insulin detemir, that for some patients, insulin degludec may also replace insulin glargine (100 or 300 IU/mL) and the combination product insulin degludec/aspart (70/30 IU/mL). The evaluation noted this was not reflected in the estimated financial impact to the PBS of listing insulin degludec.

5.6 As the resubmission stated that insulin degludec is expected to replace insulin detemir, scheduled for discontinuation in the Australian setting by the end of 2026, the evaluation considered that insulin detemir may also be a relevant comparator. The PSCR stated that any crossover period during which insulin degludec and insulin detemir were both PBS listed would be short and transitional in nature, noting

however that extensive clinical data comparing insulin degludec and insulin detemir could be provided upon request.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician submitted a written statement that discussed the management of T1D. The clinician highlighted that there is significant patient fear associated with hypoglycaemia and noted that as repeated episodes of hypoglycaemia lead to progressive blunting of the symptomatic response to hypoglycaemia, that this can lead to hypoglycaemia unawareness. The clinician indicated that minimising hypoglycaemia is a component of virtually all clinical encounters for management of the disease. The clinician suggested that insulin formulations that minimise hypoglycaemia should be favoured and highlighted the lower rates of nocturnal hypoglycaemia in randomised controlled trials for insulin degludec compared to insulin glargine 100 IU/mL.

Consumer comments

6.2 The PBAC noted and welcomed the input from the two consumer organisations, the DANII Foundation and Diabetes Alliance, and the two professional organisations, Australian Diabetes Society and the Pharmacy Guild via the Consumer Comments facility on the PBS website.

6.3 The PBAC noted that the most important clinical need for people living with T1D, according to the consumer organisations, is to have a choice of treatments. The consumer organisations indicated that choice of treatment is particularly important for people who experience nocturnal hypoglycaemia. The comments also noted that insulin degludec has shown safety in pregnancy, has a stable, flat pharmacokinetic profile (with a half-life of more than 24 hours) that can provide more consistent blood glucose management, which can in turn lead to a lower risk of hypoglycaemia compared to insulin glargine 100 IU/mL and 300 IU/mL, has benefits in young adults who may sometimes omit their prescribed insulin dose, and that treatment with insulin degludec has quality of life benefits.

6.4 The PBAC noted the advice received from the Australian Diabetes Society and the Pharmacy Guild of Australia stated that insulin degludec is likely to offer significant clinical advantages to insulin glargine and that it is important to have a long-acting insulin other than insulin glargine available.

Clinical trials

6.5 The resubmission was based on 5 head-to-head randomised trials comparing insulin degludec 100 IU/mL plus insulin aspart with insulin glargine 100 IU/mL plus insulin aspart, in patients with T1D:

- Study 3583 and Study 3770: phase 3 randomised trials previously considered by the PBAC at the March 2013 consideration of insulin degludec.
- Study 1835: a phase 2 randomised trial comparing 2 early formulations of insulin degludec with different molar concentrations to insulin glargine 100 IU/mL. This trial was not previously considered by the PBAC.
- Study 3995 (SWITCH 1) and the HypoDeg trial: 2 randomised cross-over trials comparing insulin degludec 100 IU/mL plus insulin aspart to insulin glargine 100 IU/mL plus insulin aspart, in terms of frequency of hypoglycaemia and nocturnal hypoglycaemia episodes. These trials were not previously considered by the PBAC.

6.6 The resubmission also presented brief summaries of the study design and results of 11 supportive studies in selected patient groups excluded from the key clinical trials: children <18 years (4 studies); pregnant women (1 study), real-life studies (2 studies) and long-term studies (2 studies).

6.7 In addition, the resubmission identified 2 network meta-analyses (Dawoud 2018; Martin 2021) and 11 meta-analyses, which did not identify any additional trials suitable for inclusion in the resubmission.

6.8 Details of the trials presented in the resubmission are provided in Table 3.

Table 3: Trials presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Included studies		
Study 3583 (BEGIN Basal-Bolus) (NCT00982228)	A 52-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin in subjects with type 1 diabetes.	Report date: 31 May 2011.
	Heller S., Buse J., Fisher M., 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.	The Lancet 2012; 379(9825):1489–97.
	Bode B.W., Buse J.B., Fisher M., et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN Basal–Bolus Type 1): 2-year results of a randomized clinical trial.	Diabetic Medicine 2013; 30(11):1293–1297.
Study 3770 (BEGIN FLEX T1) (NCT01079234)	A 26-week trial investigating the dosing flexibility, efficacy and safety of NN1250 in subjects with type 1 diabetes with a 26-week extension.	Report date: 27 May 2011.
	Mathieu C., Hollander P., Miranda-Palma B., et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): A 26-week randomized, treat-to-target trial with a 26-week extension.	Journal of Clinical Endocrinology Metabolism 2013; 98:1154–1162.
Study 1835 (NCT00612040)	A 16-week randomised, open labelled, 3-armed, treat-to-target, parallel group trial comparing SIBA (D) once daily + NovoRapid®, SIBA (E) once daily + NovoRapid® and insulin glargine once daily + NovoRapid®, all in a basal-bolus regimen in subjects with type 1 diabetes.	Report date: 1 April 2009.
	Birkeland K.I., Home P.D., Wendisch U., et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine.	Diabetes Care 2012; 34(3):661-665.
	Home P.D., Meneghini L., Wendisch U., et al. Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes.	Diabetic Medicine 2012; 29(6):716-720.
Study 3995 (SWITCH 1) (NCT02034513)	A randomised, double-blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes.	Report date: 3 June 2016.
	Lane W., Bailey T.S., Gerety G., et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: The SWITCH 1 randomized clinical trial.	JAMA 2017; 318(1):33-44.
HypoDeg (NCT02192450)	Pedersen-Bjergaard U., Agesen R.M., Brøsen J.M.B., et al. Comparison of treatment with insulin degludec and glargine U100 in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia: The HypoDeg randomized, controlled, open-label, crossover trial.	Diabetes Obesity and Metabolism 2022; 24(2):257-267.
	Brøsen J.M.B, Agesen R.M., Kristensen P.L., et al. Effect of insulin degludec versus insulin glargine U100 on nocturnal glycaemia assessed by plasma glucose profiles in people with type 1 diabetes prone to nocturnal severe hypoglycaemia.	Diabetes Obesity and Metabolism 2023; 25(6):1557-1565.

Source: Table 2-2, pp26-27 of the resubmission.

6.9 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Interventions	Patient population	Key primary and secondary outcomes
Study 3583	629	Phase 3, R, OL, P, MC 52 weeks	High	IDeg + IAsp, IGlar + IAsp	Adults ≥18 years diagnosis of T1D ≥12 mths on basal-bolus insulin ≥12 mths HbA1c ≤10.0%, BMI ≤35 kg/m^2	Change from baseline HbA1c, achieving glycaemic goals, rate of hypoglycaemia and nocturnal hypoglycaemia episodes, QoL outcomes, adverse events
Study 3770	493	Phase 3, R, OL, P, MC 26 weeks	High	IDeg OD FF + IAsp, IDeg OD + IAsp, IGlar + IAsp	Adults ≥18 years diagnosis of T1D ≥12 months on basal-bolus insulin ≥12 mths HbA1c ≤10.0%, BMI ≤35 kg/m^2	Change from baseline HbA1c, achieving glycaemic goals, rate of hypoglycaemia and nocturnal hypoglycaemia episodes, QoL outcomes, adverse events
Study 1835	178	Phase 2, R, OL, P, MC 16 weeks	High	IDeg + IAsp, IGlar + IAsp	Adults 18-75 years diagnosis of T1D ≥12 mths treated with insulin HbA1c 7.0-11.0%	Change from baseline HbA1c, achieving glycaemic goals, rate of hypoglycaemia and nocturnal hypoglycaemia episodes, QoL outcomes, adverse events
Study 3995	501	Phase 3, R, DB, CO MC 64 weeks	Low	IDeg + IAsp, IGlar + IAsp	Adults ≥18 years diagnosis of T1D for ≥12 mths on a basal-bolus regimen ≥26 weeks, HbA1c ≤10.0%, BMI ≤45 kg/m^2. History of hypoglycaemic episodes, hypoglycaemic symptom unawareness, or moderate CKD	Rate of severe/confirmed hypoglycaemia episodes and confirmed nocturnal hypoglycaemia episodes, change from baseline in HbA1c, QoL outcomes, adverse events
HypoDeg	149	Phase 4, R, OL, CO 24 months	High	IDeg + IAsp, IGlar + IAsp	Adults ≥18 years diagnosis of T1D ≥5 years with ≥1 severe nocturnal hypoglycaemia episode in last 2 years	Number of nocturnal symptomatic hypoglycaemia episodes, rates of any, mild symptomatic, asymptomatic and severe hypoglycaemia episodes, change from baseline in HbA1c, adverse events

Source: Table 2-6, p38 of the resubmission.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CO, cross-over; FF, fixed flexible; HbA1c, glycated haemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IGlar, insulin glargine; MC, multicentre; mths, months; OD, once daily dosing; OL, open label; P, parallel; QoL, quality of life; R, randomised; T1D type 1 diabetes.

6.10 All key trials included in the resubmission compared insulin degludec 100 IU/mL to insulin glargine 100 IU/mL in patients with T1D, in a basal-bolus regimen with insulin aspart, titrated to prespecified self-monitored plasma glucose (SMPG) FPG targets of no less than 4.0 mmol/L and no more than 5.0-6.0 mmol/L (targets were not reported in the HypoDeg trial). Children (aged <18 years), pregnant women, and patients with

a history of recent symptomatic cardiovascular disease, or proliferative retinopathy or maculopathy requiring treatment were excluded.

6.11 Study 3770 included two insulin degludec treatment arms (insulin degludec OD: once daily with the main evening meal; and insulin degludec OD FF: once daily fixed flexible dosing in a rotating schedule with approximately 8-, 24- or 40-hour intervals between doses). The insulin degludec OD FF regimen was compared to the insulin glargine (once daily with the main evening meal), and insulin degludec OD treatment arms. All regimens were administered with prandial insulin aspart (fast-acting bolus insulin).

6.12 The evaluation and the ESC considered that the risk of bias in Studies 3583, 3770, 1835 and the HypoDeg trial was high, given the open label trial designs, noting that the risk of bias may be minimised for more objective outcomes such as measures of glycaemic control (HbA1c or fasting plasma glucose). The evaluation and the ESC considered that knowledge of treatment assignment may affect disease management decisions (dose titration) and other outcomes that depend on self-reported assessments. The PSCR stated that the sponsor disagreed with this assessment of the risk of bias, which appeared to have been based on blinding of investigators and participants. The PSCR argued that using the multi-component Cochrane Risk of Bias tool that the overall risk of bias was assessed as low for studies 3583, 3770 and 1835, with some concerns for HypoDeg due mainly to the lack of information regarding methods for measuring and managing missing data.

6.13 The risk of bias in Study 3995 was unclear, given insulin degludec and insulin glargine have different pharmacokinetic and time-action profiles, and the timing of insulin administration could potentially affect the time interval during which subjects would be at highest risk of experiencing hypoglycaemia episodes. The risk of bias may be reduced as subjects were randomised 1:1 to morning and evening dosing; however, the impact of these differences remained unclear.

6.14 Larger proportions of patients treated with insulin degludec discontinued compared to those treated with insulin glargine in Study 3770 (insulin degludec fixed flexible dosing 15.8%; insulin degludec once daily 15.9%; insulin glargine 7.3%), and the HypoDeg trial (insulin degludec 23.3%; insulin glargine 5.3%). The most common reasons for study discontinuation were adverse events, ineffective therapy or other reasons (not defined).

6.15 The evaluation and the ESC noted that Study 3995 and the HypoDeg trial included patients prone to hypoglycaemia episodes, nocturnal hypoglycaemia episodes or experiencing hypoglycaemic unawareness. This was consistent with the primary study objectives of investigating differences in the rate of hypoglycaemia episodes between basal insulin regimens in patients with T1D.

6.16 Study 3995 and the HypoDeg trial also included larger proportions of patients previously treated with insulin detemir at baseline (Study 3995: 58.4-63.5%; HypoDeg: 40%) compared with other studies (Study 3583: 18.4-21.7%; Study 3770: 26.1-28.7%;

Study 1835: 28.1%), and smaller proportions using insulin glargine at baseline (Study 3995: 0-0.4%; HypoDeg: 35%) compared with other studies (Study 3583: 68.8-70.8%; Study 3770: 64.8-65.2%; Study 1835: 52.2%). Study 3995 also included smaller proportions of patients using once daily basal insulin regimens (42.6-46.8%) and larger proportions using continuous subcutaneous insulin infusions (17.3-21.4%) compared to other studies (Study 3583: OD 71.3-73.9%, CSII 1.9-2.1%; Study 3770: OD 68.3-70.9%, CSII excluded; Study 1835: OD 50.0-56.0%; CSII 3.4-5.0%).

6.17 The evaluation and the ESC noted that the patient demographic and disease characteristics of Studies 3583, 3770, 1835 and 3995 were similar to the Australian T1D population in the Australian Diabetes Clinical Quality (ADCQ) registry Annual Report 2024 in terms of mean age (42.6-47.2 years versus 45.8 years), and median duration of T1D (17.3-23.6 years versus 18.9 years). However, patients in the HypoDeg trial were older (mean age 54 years), and had a longer duration of T1D (median duration 28 years). Baseline HbA1c in Studies 3583, 3770, and 3995 and the HypoDeg trial were lower compared to the Australian T1D population in the ADCQ registry (HbA1c 7.5-7.8% versus 8.0%), while in Study 1835 baseline HbA1c was higher (HbA1c 8.3-8.5%). In the Australian T1D population in the ADCQ registry, only a small proportion of patients reported any episodes of severe hypoglycaemia (6.6%), with 3.9% reporting 1-2 episodes, 1.7% reporting 3-5 episodes, and 1.1% reporting more than 5 episodes.

6.18 All studies included in the resubmission used basal-bolus insulin regimens with SMPG data for insulin titration and hypoglycaemia outcomes, with plasma glucose measured by glucose meter and capillary blood test strips. In Study 3583, continuous glucose monitoring (CGM) was used to measure interstitial glucose in a subset of 165 (26%) patients at randomisation, and 140 (22%) patients at Week 52. However, 88.9% of the Australian T1D population in the ADCQ registry used CGM and 80.5% used CGM only, while 19.7% used capillary blood test strips either alone, or in combination with CGM. Studies 3583, 3770, 1835 and 3995 were conducted more than a decade ago, and may no longer reflect current clinical practice, with substantial use of CGM affecting monitoring of hypoglycaemia episodes and insulin dosing. The PSCR acknowledged the limitations of the evidence base but indicated that given the stage of the life cycle for insulin degludec, additional trials are not likely to be conducted.

Comparative effectiveness

Glycaemic control

6.19 **Table 5** summarises the results of Studies 3853, 3770, 1853 and 3995 for least squares mean difference in change in HbA1c from baseline, between insulin degludec and insulin glargine, both in combination with prandial insulin aspart.

Table 5: Change in HbA1c (%) from baseline

	Insulin degludec			Insulin glargine			IDeg vs IGlar, LSM difference, % (95% CI)
	Baseline HbA1c (%) mean (SD)	Endpoint HbA1c (%) mean (SE)	LSM change from baseline, % (SE)	Baseline HbA1c (%) mean (SD)	Endpoint HbA1c (%) mean (SE)	LSM change from baseline, % (SE)	
Study 3583 (52 weeks)	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)
Study 3770[a] (26 weeks)							
IDeg OD FF	N=164 7.7 (1.0)	7.31 (0.05)	-0.40 (0.05)	N=164 7.7 (0.9)	7.14 (0.05)	-0.57 (0.05)	0.17 (0.04, 0.30)
IDeg OD	N=165 7.7 (1.0)	7.30 (0.05)	-0.41 (0.05)				NR[a]
Study 1835 (16 weeks)[b]	N=59 8.4 (0.9)	7.87 (0.09)	-0.53 (0.09)	N=59 8.3 (0.8)	7.76 (0.09)	-0.64 (0.09)	0.10 (-0.14, 0.34)
Study 3995 (32 weeks)							
Period 1 (to 32 weeks)	N=249 7.66 (1.05)	6.80 (0.06)	-0.76 (0.06)	N=252 7.49 (0.98)	6.77 (0.07)	-0.78 (0.07)	0.03 (-0.10, 0.15)
Period 2 (32-64 weeks)	N=205 6.78 (0.81)	6.94 (0.06)	0.09 (0.06)	N=209 6.92 (0.92)	6.83 (0.06)	-0.02 (0.06)	0.11 (-0.00, 0.23)

Source: Table 2-20, p51; Table 2-25, p59; Table 2-31, p64; Table 2-38, p74 of the resubmission; Table 14.2.44, p403 and Table 11-7, p116 of Study 3583 CSR; Table 14.2.39, p338 and Table 11-8, p107 of Study 3770 CSR; Table 14.2.55, p230 and Table 11-6, p83 of Study 1835 CSR; Table 14.2.94, pp544-545, Table 14.2.97, p556 and Table 14.2.99, p559 of Study 3995 CSR.

Abbreviations: CI, confidence interval; FF, fixed flexible; HbA1c, glycated haemoglobin; IDeg, insulin degludec; IGlar, insulin glargine; LSM, least squares mean; NR, not reported; OD, once daily; SD, standard deviation; SE, standard error.

[a] Comparative analyses of insulin degludec (once daily) versus insulin glargine were not conducted in Study 3770.

[b] Study 1835 included 2 formulations of insulin degludec with different molar concentrations (600 µmol/L and 900 µmol/L). Results presented herein are for the 600 µmol/L formulation, which was carried forward to the phase 3 trials and registration.

6.20 Studies 3583, 3770, 1835 and 3995 showed there was no statistically significant difference in mean change in HbA1c from baseline between insulin degludec and insulin glargine, both given in combination with prandial insulin aspart.

6.21 The ESC noted that the PBAC has previously used a non-inferiority margin for difference in HbA1c of 0.3 to 0.4% in the treatment of T1D (para 7.4, Insulin Glargine PSD, July 2015 PBAC meeting). The ESC further noted that all comparisons demonstrated the non-inferiority of insulin degludec to insulin glargine, with an upper limit of the 95% confidence interval ≤ 0.4%.

6.22 In the HypoDeg trial, mean baseline HbA1c was 7.8% (± 0.9%). Mean HbA1c for patients treated with insulin degludec was 7.9% (± 0.9%) in the first 9-month treatment period and 7.9% (± 0.9%) in the second 9-month crossover maintenance period, with no statistically significant difference compared to patients treated with insulin glargine; HbA1c 7.7% (± 0.9%) 1st treatment period; 8.0% (± 0.9%) 2nd treatment period).

6.23 Studies 3853, 3770, and 1853 assessed the difference between insulin degludec and insulin glargine in the proportions of patients achieving glycaemic targets. HbA1c response was not reported in the HypoDeg trial. Larger proportions of patients in Studies 3583 and 3770 treated with insulin glargine achieved a HbA1c <7%, compared

to insulin degludec, but the differences were small and not statistically significant. In Study 1835, a larger proportion of patients treated with insulin degludec achieved HbA1c <7% compared to insulin glargine, but the difference between arms was not formally assessed.

6.24 In Studies 3583, 3770 and 1835, mean FPG decreased in all treatment groups over the treatment periods, and differences in FPG between insulin degludec and insulin glargine were small, and not statistically significant (Study 3583 after 52 weeks: FPG -0.33 mmol/L, 95% CI: -1.03; 0.36; Study 3770 after 26 weeks: FPG -0.05 mmol/L, 95% CI: -0.85, 0.76; Study 1835 after 16 weeks: FPG -0.56 mmol/L, 95% CI: -1.84, 0.73).

6.25 FPG was reported using descriptive statistics only in Study 3995 and was not reported in the HypoDeg trial.

Hypoglycaemia episodes

6.26 Table 6 summarises the differences in rates of hypoglycaemia episodes between insulin degludec and insulin glargine in Studies 3853, 3770, 1853, and 3995.

Table 6: Difference in rate of hypoglycaemia episodes (Studies 3583, 3770, 1835, 3995; FAS)

	IDeg LSM episodes/100 PY	IGlar LSM episodes/100 PY	IDeg vs IGlar, treatment ratio (95% CI)
Study 3583 (52 weeks)	N=472	N=157	-
Confirmed hypoglycaemia	4460.12	4177.82	1.07 (0.89, 1.28)
Severe hypoglycaemia	19.16	13.92	1.38 (0.72, 2.64)
Confirmed nocturnal hypoglycaemia	413.66	548.20	0.75 (0.59, 0.96)
Study 3770 (26 weeks) IDeg OD FF	N=164	N=164	-
Confirmed hypoglycaemia	7954.68	7709.88	1.03 (0.85, 1.26)
Severe hypoglycaemia	33.53	37.79	0.89 (0.40, 1.99)
Confirmed nocturnal hypoglycaemia	598.70	990.67	0.60 (0.44, 0.82)
Study 3770 (26 weeks) IDeg OD[a]	N=165	N=164	-
Confirmed hypoglycaemia	8629.14	7709.88	NR[a]
Severe hypoglycaemia	30.84	37.79	
Confirmed nocturnal hypoglycaemia	950.26	990.67	
Study 1835 (16 weeks) IDeg OD	N=59	N=59	-
All hypoglycaemia, episodes/100 PY	100.8	117.8	0.86 (0.66, 1.12)
Major hypoglycaemia, episodes/100 PY	0	0	0.99 (0.22, 4.52)
Major/minor hypoglycaemia, episodes/100 PY	47.88	66.22	0.72 (0.52, 1.00)
Study 3995 (32 weeks) Period 1	N=418	N=422	-
Severe/BG confirmed symptomatic hypoglycaemia	1227.03	1372.32	**0.89 (0.85, 0.94)**
Nocturnal severe/BG confirmed symptomatic hypoglycaemia	160.16	250.77	**0.64 (0.56, 0.73)**

Source: Table 2-22, p53; Table 2-27, p60; Table 2-33, p66; Table 2-36 to 2-37, p74 of the resubmission.
Abbreviations: CI, confidence interval; FAS, full analysis set; FF, fixed flexible; IDeg, insulin degludec; IGlar, insulin glargine; LSM, least squares mean; OD, once daily; PY, patient years.
[a] Comparative analyses of insulin degludec (once daily) versus insulin glargine were not conducted in Study 3770.
Note: Statistically significant results in bold.

6.27 In Studies 3583, 3770 and 1835, the differences in rates of confirmed hypoglycaemia episodes, severe hypoglycaemia episodes, all hypoglycaemia episodes and

major/minor hypoglycaemia episodes between treatments were small, and not statistically significantly different between arms. The rates of severe hypoglycaemia episodes in Studies 3583 and 3770 were generally lower in patients treated with insulin degludec compared to insulin glargine, but large proportions of patients in both treatment groups (>85%) did not report any severe hypoglycaemia episodes.

6.28 In Study 3995, statistically significantly lower rates of confirmed nocturnal hypoglycaemia episodes, confirmed severe nocturnal hypoglycaemia episodes and confirmed severe hypoglycaemia episodes were experienced by patients treated with insulin degludec compared to insulin glargine. In Studies 3583 and 3770, nominally significantly lower rates of confirmed nocturnal hypoglycaemia episodes and confirmed severe nocturnal episodes were experienced by patients treated with insulin degludec compared to insulin glargine.

6.29 Confirmed hypoglycaemia episodes and confirmed nocturnal hypoglycaemia episodes covered a broad range of hypoglycaemia experiences, from hypoglycaemia episodes requiring intervention and the assistance of another person, to symptomatic or asymptomatic hypoglycaemia episodes requiring no intervention or assistance. The evaluation and the ESC noted that Study 3995 included patients prone to hypoglycaemia episodes and therefore that the rates of episodes reported are not comparable the rates reported in Studies 3583, 3770 and 1835. The evaluation and the ESC further noted that the comparative hypoglycaemia outcomes in Study 3770 only included patients randomised to a fixed-flexible dosing regimen, not used in the other trials or commonly in clinical practice and may have been impacted by differences in pharmacokinetic and time-action profiles between insulin degludec and insulin glargine.

6.30 Table 7 summarises the differences in rates of hypoglycaemia episodes between insulin degludec and insulin glargine in the HypoDeg trial.

Table 7: Difference in rate per year of hypoglycaemia episodes (HypoDeg; FAS)

	IDeg N=73		IGlar N=76		IDeg vs IGlar
	Episodes	Episodes/PY mean (SD)	Episodes	Episodes/PY mean (SD)	RRR (95% CI)
Nocturnal symptomatic hypoglycaemia in maintenance periods					
Level 1 (PG ≤3.9 mmol/L)					
12:00am-05:59am	319	2.88 (5.14)	408	3.87 (5.84)	**28% (9, 43)**
11:00pm-06:59am	622	5.69 (8.68)	757	7.39 (9.31)	**28% (4, 45)**
Level 2 (PG ≤3.0 mmol/L)					
12:00am-05:59am	186	1.68 (3.61)	261	2.47 (4.26)	**37% (16, 53)**
11:00pm-06:59am	316	2.87 (5.36)	427	4.14 (6.18)	**34% (17, 48)**
Severe symptomatic hypoglycaemia in maintenance periods					
All day (24 hours)	56	0.52 (1.26)	80	0.85 (1.78)	**35% (1, 58)**
Daytime					
06:00am-12:00am	41	0.38 (1.02)	46	0.45 (1.23)	10% (-73, 53)
07:00am-12:00pm	36	0.34 (0.96)	42	0.41 (1.21)	13% (-86, 79)
Nocturnal					
00:00am-06:00am	14	0.13 (0.42)	33	0.40 (1.26)	52% (-10, 79)
11:00pm-07:00am	19	0.17 (0.54)	37	0.43 (1.30)	51% (-15, 79)

Source: Table 2-41 and Table 2-42, p80 of the resubmission.
Abbreviations: FAS, full analysis set; IDeg, insulin degludec; IGlar, insulin glargine; PG, plasma glucose; PY, patient-year; RRR, relative rate reduction; SD, standard deviation.
Note: Statistical analyses were descriptive, based on a 5% (two-sided) level of statistical significance with no adjustment for multiple testing.

6.31 Patients treated with insulin degludec experienced statistically significantly lower rates of level 1 (plasma glucose (PG) ≤3.9 mmol/L) and level 2 (PG ≤3.0 mmol/L) nocturnal symptomatic hypoglycaemia compared to insulin glargine for both nocturnal time periods, as well as a statistically significantly lower rate of all day (24 hours) severe symptomatic hypoglycaemia. There were no statistically significant differences between treatments in severe symptomatic daytime or nocturnal hypoglycaemia over the specified time periods. The ESC considered the extent of any benefit to be uncertain given the increased use of continuous glucose monitoring in clinical practice (89% according to the ADCQ registry versus 26% in the trials).

6.32 The ESC noted that the HypoDeg trial only included patients prone to hypoglycaemia episodes, and the rates of episodes reported could not be directly compared to Studies 3583, 3770 and 1835.

Patient reported outcomes

6.33 Studies 3583, 1835 and 3995 collated SF-36 data, and did not identify any statistically significant differences between treatment arms in overall scores. Similarly, Studies 3583 and 3995 collated Treatment Related Impact Measure – Diabetes (TRIM-D) data and found improved treatment related impact in both treatment groups, but no statistically significant differences between treatment arms.

Insulin dose

6.34 In Studies 3583 and 3770 mean insulin degludec doses were lower compared to insulin glargine. However, in Study 1835 mean insulin glargine doses were lower compared to insulin degludec, while in Study 3995 mean insulin glargine doses were lower

compared to insulin degludec at the end of period 1, but higher than insulin degludec at the end of period 2. In Study 3995, differences in insulin doses between treatment groups were reduced when adjusted for baseline differences in body weight. Differences in mean insulin dose between insulin degludec and insulin glargine varied between trials but were similar for both treatments.

6.35 In the HypoDeg trial mean total insulin dose during treatment was similar between insulin degludec (42.7 IU) and insulin glargine (42.5 IU) at the end of the first treatment period, and the second maintenance period (49.2 IU; 48.1 IU). In a linear mixed effects model the mean total insulin dose was statistically significantly lower with insulin degludec. Similar results were observed for basal insulin doses (1st treatment period 21.3 IU, 19.4 IU; 2nd treatment period 24.6 IU, 24.1 IU), with the difference in basal insulin doses being statistically significantly lower with insulin degludec.

6.36 The mean ratio of insulin degludec to insulin glargine 100 IU/mL for basal insulin was reported to be 0.91 IU/kg in Study 3583, based on the ratio of mean doses of insulin degludec to insulin glargine at last treatment visit. The Pre-PBAC response proposed the equi-effective dose of insulin degludec to insulin glargine (100 IU/mL) to be 0.86:1.00, based on the estimated treatment ratio of insulin degludec to insulin glargine at Week 52 as reported in Table 2 of the Heller et al., 2012 publication of Study 3583. This ratio was estimated by use of ANOVA of log-transformed dose value (U/kg) at week 52 with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and week 1 dose as covariates.

Network meta-analyses

6.37 The ESC noted that the results of the network meta-analyses investigating the comparative efficacy and safety of basal insulin regimens in adults with T1D (Dawoud 2018; Martin 2021) generally showed no statistically significant differences between insulin degludec and insulin glargine in terms of glycaemic control and hypoglycaemia episodes.

Supportive evidence

6.38 The ESC noted that the supportive evidence presented in the resubmission for the use of insulin degludec in children (Thalange 2015; Elhabashy 2023; Nally 2023; Urakami 2017) suggested that insulin degludec demonstrates similar efficacy and safety compared to other long-acting insulin analogues. Similarly, Mathiesen (2023; EXACT trial), found that insulin degludec was non-inferior to insulin detemir in pregnant women in terms of efficacy and safety, with no significant differences between treatment groups for hypoglycaemia episodes (any, nocturnal, or severe) or for maternal adverse events and serious adverse events.

6.39 Bode (2013), a 12-month extension of Study 3583, found that HbA1c over 104 weeks was similar between insulin degludec and insulin glargine, with small reductions compared to the end of the Study 3583 treatment period. The rate of nocturnal

confirmed hypoglycaemia was significantly lower with insulin degludec compared to insulin glargine, with an estimated rate ratio (insulin degludec/insulin glargine) of 0.75 (95% CI 0.59, 0.95), similar to the Study 3583 results, and the rates of overall confirmed hypoglycaemia were similar in both treatment arms, and not statistically significantly different. The evaluation and the ESC noted that the daily insulin dose was significantly lower with insulin degludec compared to insulin glargine at the end of 104 weeks. Safety outcomes were similar between treatment arms.

6.40 Mathieu (2013), a 6-month extension of Study 3770, found no statistically significant difference between treatments in HbA1c, and confirmed hypoglycaemia rates were similar between treatment arms. Nocturnal confirmed hypoglycaemia rates were 25% lower with insulin degludec compared to insulin glargine at Week 52. At Week 52, mean daily basal, bolus and total insulin doses were lower in the insulin degludec arm than the insulin glargine arm. However, the evaluation and the ESC noted that results of the extension study were for the insulin degludec free-flexible formulation, and use of this dosing regimen in the Australian setting is uncertain.

Comparative harms

6.41 **Table 8** summarises the key treatment emergent adverse events reported in Studies 3583, 3770, 1835 and 3995. The HypoDeg trial did not report adverse events.

Table 8: Summary of key adverse events in the randomised trials (SAS)

Trial ID	3583		3770			1835		3995	
	IDeg	IGlar	IDeg FF	IDeg OD	IGlar	IDeg OD	IGlar	IDeg	IGlar
Summary of key treatment emergent adverse events, n (%)									
N	472	154	164	165	161	59	59	454	460
Any TEAEs	397 (84.1)	128 (83.1)	111 (67.7)	125 (75.8)	116 (72.2)	45 (76.3)	39 (66.1)	294 (64.8)	310 (67.4)
Serious TEAEs	49 (10.4)	17 (11.0)	9 (5.5)	7 (4.2)	8 (5.0)	2 (3.4)	1 (1.7)	58 (12.8)	70 (15.2)
Severe TEAEs	75 (15.9)	24 (15.6)	13 (11.6)	24 (14.5)	20 (12.2)	4 (6.8)	1 (1.7)	43 (9.5)	67 (14.6)
Moderate TEAEs	201 (42.6)	60 (39.0)	46 (28.0)	45 (27.3)	51 (31.7)	24 (40.7)	19 (32.2)	119 (26.2)	132 (38.7)
Basal insulin related AEs	112 (22.7)	27 (17.5)	41 (25.0)	34 (20.6)	30 (18.6)	7 (11.9)	3 (5.1)	58 (12.8)	61 (13.3)
Bolus insulin related AEs	109 (23.1)	31 (20.1)	40 (24.4)	27 (16.4)	26 (16.2)	4 (6.8)	2 (3.4)	NR	NR
Withdrawal due to AE	12 (2.5)	2 (1.3)	5 (3.0)	4 (2.4)	1 (0.6)	2 (3.4)	1 (1.7)	9 (2.0)	7 (1.5)
Treatment emergent adverse events (≥5% of patients), n (%)									
Hypoglycaemia	51 (10.8)	12 (7.8)	11 (6.7)	18 (10.9)	10 (6.2)	-	-	17 (3.7)	33 (7.2)
Nasopharyngitis	130 (27.5)	6 (3.9)	31 (18.9)	43 (26.1)	29 (18.0)	24 (40.7)	15 (25.4)	68 (15.0)	61 (13.3)
Headache	68 (14.4)	21 (13.6)	10 (6.1)	16 (9.7)	18 (11.2)	16 (27.1)	10 (16.9)	-	-
Gastroenteritis	29 (6.1)	4 (2.6)	-	-	-	3 (5.1)	2 (3.4)	-	-
Influenza	33 (7.0)	15 (9.7)	-	-	-	6 (10.2)	3 (5.1)	-	-
Sinusitis	37 (7.8)	13 (8.4)	-	-	-	NR	4 (6.8)	-	-
URTI	94 (19.9)	23 (14.9)	6 (3.7)	9 (5.5)	13 (8.1)	2 (3.4)	7 (11.9)	29 (6.4)	39 (8.5)
UTI	25 (5.3)	8 (5.2)	-	-	-	-	-	-	-
Diarrhoea	25 (5.3)	7 (4.5)	4 (2.4)	4 (2.4)	9 (5.6)	2 (3.4)	4 (6.8)	-	-
Nausea	26 (5.5)	10 (6.5)	9 (5.5)	7 (4.2)	8 (5.0)	5 (8.5)	2 (3.4)	-	-
Vomiting	16 (3.4)	8 (5.2)	4 (2.4)	9 (5.5)	5 (3.1)	-	-	-	-
Constipation	-	-	-	-	-	3 (5.1)	1 (1.7)	-	-
Cough	23 (4.9)	11 (7.1)	7 (4.3)	4 (2.4)	10 (6.2)	-	-	-	-
Bronchitis	18 (3.8)	8 (5.2)	-	-	-	-	-	-	-
Wrong drug administered	25 (5.3)	5 (3.2)	9 (5.5)	9 (5.5)	7 (4.3)	-	-	-	-

Source: Tables 2-24, 2-30, 2-35, and 2-40, pp57-78 of the resubmission; Table 14.3.1.3, p756 of the Study 3583 CSR; Table 12-8, p135 of the Study 3770 CSR; Table 14.3.1.4, p311 of the Study 1835 CSR; Table 14.3.1.3, p1021 of the Study 3995 CSR.

Abbreviations: CSR, clinical study report; FF, fixed flexible; IDeg, insulin degludec; IGlar, insulin glargine; OD, once daily; SAS, safety analysis set; TEAE, treatment emergent adverse events; URTI, upper respiratory tract infection; UTI, urinary tract infection.

6.42 Large proportions of patients reported at least one adverse event in all studies (64.8-84.1%), with similar proportions of patients with serious adverse events and severe adverse events in both treatment arms. The most frequently reported treatment emergent adverse events in both treatment groups across all studies were nasopharyngitis, headache, upper respiratory tract infection, hypoglycaemia, influenza, nausea and sinusitis.

6.43 In Studies 3583, 3770 and 1835, larger proportions of patients treated with insulin degludec reported nasopharyngitis compared to insulin glargine.

6.44 Overall, the proportions of patients reporting adverse events appeared similar between treatment arms.

Benefits/harms

6.45 A benefits/harms table was not presented as the resubmission made a claim of non-inferior comparative effectiveness and safety.

Clinical claim

6.46 The resubmission described insulin degludec as non-inferior in terms of effectiveness and safety compared with insulin glargine 100 IU/mL, with potentially important clinical advantages in nocturnal hypoglycaemia, basal and total insulin doses, flexibility of administration times and use in critical early childhood and pregnancy.

6.47 The ESC considered that the therapeutic conclusions presented in the resubmission were adequately supported by the evidence presented in the resubmission in terms of non-inferior efficacy and safety, but that the claimed clinical advantages were not supported for the following reasons:

- Results of the clinical trials generally showed a reduction in the rates of nocturnal hypoglycaemia events in patients treated with insulin degludec compared to insulin glargine. However, the evaluation and the ESC considered that the magnitude of benefit likely to be realised in the Australian setting is uncertain, given:
  - the clinical outcomes in Studies 3583 and 3770 included asymptomatic episodes of nocturnal hypoglycaemia requiring little or no intervention.
  - Study 3995 and the HypoDeg trial were conducted in enriched populations of T1D patients prone to hypoglycaemia episodes, and the results of these trials may not be applicable to the broader Australian target population.
  - comparative results from Study 3770 were only presented for patients randomised to an insulin degludec fixed-flexible dosing regimen, which is not likely to be applicable the Australian setting.
  - Studies 3583, 3770, 1835 and 3995 were conducted more than a decade ago, and may no longer reflect current clinical practice, with substantial use of CGM affecting monitoring of hypoglycaemia episodes and insulin dosing in the Australian setting.
- The clinical evidence supporting the use of insulin degludec in children suggests insulin degludec demonstrates similar efficacy and safety compared to other long-acting insulin analogues. Insulin glargine and other insulin analogues are safely used in children aged ≥1 year[1]. The PSCR stated that the claim relating to age

[1] Clinical practice guidelines: Diabetes mellitus, Royal Children's Hospital Melbourne; UpToDate: Type 1 diabetes mellitus in children and adolescents, Insulin therapy, Accessed 5 May 2025

related primarily to the quality of evidence supporting use in younger paediatric patients, and that for insulin glargine 100 IU/mL, the evidence in children aged from 2 to 5 years was inconclusive. The ESC considered that the clinical evidence supporting use of insulin degludec in children suggests that it demonstrates similar efficacy and safety compared to other long-acting insulin analogues. The ESC noted that insulin glargine and other insulin analogues are safely used in children aged ≥1 year, and that the TGA approval for insulin glargine 100 IU/mL does not limit use based on age. The ESC therefore considered that the resubmission's argument was not supported.

- The use of insulin degludec during pregnancy was under consideration by the TGA at the time of the ESC meeting. The supportive clinical trial (EXACT) presented in the resubmission found insulin degludec was non-inferior to insulin detemir in pregnant women in terms of efficacy and safety. The PSCR stated that the sponsor is "not claiming that insulin degludec is any safter than insulin glargine [100 IU/mL] in pregnancy but that its safety is supported by the highest quality randomised controlled trial evidence". The ESC noted that insulin glargine and other insulin analogues are currently safely used in pregnancy.
- The ESC noted that the evidence for total daily insulin requirements was not consistent between clinical trials, with some studies showing lower mean total insulin doses for insulin degludec compared to insulin glargine (Studies 3583, 3770, HypoDeg), and others showing lower insulin glargine dose compared to insulin degludec (Studies 1835, 3995). The ESC noted that differences in mean insulin dose between insulin degludec and insulin glargine 100 IU/mL varied between the trials but were similar for both treatments. The ESC noted that while results from Study 3770 and Study 3583 (and their extension studies) suggested the daily dose of insulin degludec would be lower than insulin glargine 100 IU/mL, the results of other studies did not.

6.48 The PBAC considered that the claim that insulin degludec 100 IU/mL has at least non-inferior comparative effectiveness to insulin glargine 100 IU/mL was reasonable.

6.49 The PBAC considered that the claim that insulin degludec 100 IU/mL has at least non-inferior comparative safety compared to insulin glargine 100 IU/mL was reasonable.

Economic analysis

The resubmission presented a simple cost consequences analysis, listing the comparative per-unit costs of insulin degludec 100 IU/mL versus insulin glargine 100 IU/mL, and the potential advantages of insulin degludec to the target population of T1D patients, if insulin degludec were listed on the PBS. The PBAC Guidelines state that, generally, a cost consequences analysis should not be presented on its own but may be useful as a supplementary or preliminary analysis to a cost-effectiveness or cost-utility analysis (PBAC

Guidelines V5.0, p64). The evaluation and the ESC considered that use of a cost consequences analysis was not adequately justified in the resubmission.

6.50 Table 9 summarises the cost-consequences analysis presented in the resubmission.

Table 9: Cost consequences analysis

	Insulin degludec	Insulin glargine	Increment
Costs			
DPMQ for 7,500 IU	$[redacted] or $[redacted][a]	$187.42	$[redacted]
Consequences			
- At least non-inferior glycaemic control. - Lower rates of overall and nocturnal hypoglycaemia. - Pharmacological profile with longer half-life and less day-to-day variability, more flexibility in relation to dose timing and associated improvements in adherence. - Typically, lower total daily dose requirements when used in a treat to target regimen. - Acceptable adverse event profile similar to other long-acting insulins. - Treatment for children aged ≥1 year. - An effective and safe option for diabetes in pregnancy based on high clinical trial evidence in pregnant women with T1D. - Availability of various pen devices, including NovoPen® 6 which is a connected durable device to aid patient safety.			

Source: Table 3-1, p93 of the resubmission.

Abbreviations: DPMQ, dispensed price for maximum quantity; EMP, ex-manufacturer price; IU, International Units; T1D, type 1 diabetes.

[a] The effective DPMQ proposed in the resubmission of $[redacted] included markups calculated based on an EMP of $[redacted] (calculated from the published DPMQ). It was recalculated during the evaluation to $[redacted] based on the insulin degludec effective maximum quantity EMP of $[redacted].

6.51 The evaluation and the ESC noted that the simple cost consequences analysis did not include quantification of the benefits claimed to accrue to T1D patients in the Australian setting and considered that it was difficult to interpret. The resubmission estimated a difference in the price of insulin detemir and insulin glargine of $[redacted] ($[redacted] - $187.42) based on an effective DPMQ for insulin degludec with markups calculated based on the published EMP rather than the effective EMP for insulin degludec. After recalculating the proposed effective DPMQ, the difference in cost between insulin degludec 100 IU/mL and insulin glargine 100 IU/mL was smaller than estimated in the resubmission ($[redacted] - $187.42 = $[redacted]). The difference in cost was similar when compared to insulin detemir 100 IU/mL ($[redacted] - $[redacted] = $[redacted]).

6.52 The resubmission proposed that the higher proposed price for insulin degludec could be considered acceptably cost effective given the small and high need target patient population, unique characteristics of insulin degludec compared to other available therapies, and important clinical/practical advantages it would provide for patients (see Table 9).

6.53 The evaluation and the ESC considered that the additional benefits claimed to accrue to T1D patients in the Australian setting with the proposed PBS listing of insulin degludec were not adequately justified:

- The evaluation and the ESC considered that the claim that insulin degludec provides lower rates of overall hypoglycaemia episodes was not adequately

justified. While the evaluation and the ESC considered that the evidence provided in the resubmission supported a reduction in nocturnal hypoglycaemia episodes compared to insulin glargine, the ESC considered the magnitude of benefit in Australian clinical practice to be unclear given the effect that higher rates of continuous glucose monitoring (88.9% of patients in the ADCQ registry compared to 26% of patients in Study 3585 at randomisation and 22% at week 52) might have on monitoring of hypoglycaemia episodes and insulin dosing in clinical practice.

- The resubmission claimed that a higher price for insulin degludec was reasonable given it can be used in children 1 year and older whereas the data to support the use of insulin glargine 100 IU/mL in children aged 2 to 5 years was inconclusive. The ESC considered that the clinical evidence supporting use of insulin degludec in children suggests that it demonstrates similar efficacy and safety compared to other long-acting insulin analogues. The ESC noted that insulin glargine and other insulin analogues are safely used in children aged ≥1 year, and that the TGA approval for insulin glargine 100 IU/mL does not limit use based on age. The ESC therefore considered that the resubmission's argument was not supported.
- The use of insulin degludec during pregnancy was under consideration by the TGA at the time of the ESC meeting. The supportive clinical trial (EXACT) presented in the resubmission found insulin degludec was non-inferior to insulin detemir in pregnant women in terms of efficacy and safety. The resubmission claimed that a higher price for insulin degludec was reasonable for having an "effective and safe option for use in pregnant women". The ESC noted that the TGA was assessing the sponsor's request to change the pregnancy category for insulin degludec from Category B3 to Category A. The ESC noted that while insulin glargine is Category B3 in pregnancy, it is utilised safely in pregnant patients with T1D in Australia. The ESC considered that a higher price for this consequence was not supported.
- The resubmission claimed that insulin degludec improves adherence, and that it has the advantages of flexible dosing and lower insulin dose requirements. The ESC noted that differences in mean insulin dose between insulin degludec and insulin glargine 100 IU/mL varied between the trials but were similar for both treatments. The ESC further noted that Study 3770 had a fixed flexible dosing arm for insulin degludec which was not relevant to this resubmission. The ESC considered that a higher price for these consequences was not supported.
- The evaluation noted that pre-filled pen devices are available for other insulin analogues.

6.54 The ESC considered that a CMA to insulin glargine would be appropriate as there was no basis to support the proposed price premium using the descriptive cost

consequences analysis. The ESC requested equi-effective doses for insulin degludec 100 IU/mL and insulin glargine 100 IU/mL, and insulin degludec 100 IU/mL and insulin glargine 300 IU/mL be presented in the pre-PBAC response for consideration.

6.55 The Pre-PBAC response stated that estimation of equi-effective doses for insulin degludec 100 IU/mL and the respective insulin glargine formulations is not straightforward. The response noted that there was some heterogeneity between trials in relation to both basal and total insulin dose requirements with insulin degludec 100 IU/mL and insulin glargine 100 IU/mL, which was very likely due to differences in study design. The response stated that similar issues arise when considering available evidence comparing the insulin degludec 100 IU/mL and insulin glargine 300 IU/mL formulations. Notwithstanding, the Pre-PBAC response proposed the following equi-effective doses:

- 0.86 IU of insulin degludec (100 IU/mL) is equivalent to 1.00 IU of insulin glargine (100 IU/mL) based on results from Study 3583 (Heller et al., 2012), Table 2; and
- 0.826 IU of insulin degludec (100 IU/mL) is equivalent to 1:00 IU of insulin glargine (300 IU/mL) based on the results for the cohort of patients switching from insulin detemir in the INEOX trial (Ruiz de Adana et al., 2023) Figure S3.

Drug cost/patient

6.56 The resubmission proposed an effective DPMQ of $[redacted]. The recalculated effective DPMQ for insulin degludec was $[redacted] (based on the proposed effective AEMP for the maximum quantity of $[redacted], using standard methods). The calculation of insulin degludec drug costs were consistent between the economic and budget impact models.

Estimated PBS usage & financial implications

6.57 This resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the utilisation and financial impact of listing insulin degludec on the PBS, for the treatment of patients with T1D.

6.58 The resubmission noted that insulin detemir will be delisted from the PBS and removed from the market at the end of 2026 (Year 1). It was assumed that patients currently treated with insulin detemir would switch to insulin glargine 100 IU/mL, as the most similar long-acting basal insulin listed on the PBS. The resubmission argued that if insulin degludec is listed on the PBS, all patients currently treated with insulin detemir would instead switch to insulin degludec, as the basal insulin most similar in action to insulin detemir. Therefore, the resubmission estimated the difference in costs to the PBS between the estimated use of insulin degludec and insulin glargine over the first 6 years of listing, as the incremental cost of degludec to the PBS.

6.59 Table 10 summarises the key inputs for financial estimates presented in the resubmission.

Table 10: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Insulin detemir scripts	30,165 in 2023	PBS utilisation of insulin detemir for the 2023 calendar year (PBS items 12236B, 9040T).	The use of the single calendar year 2023 was not reasonable. The numbers of PBS insulin detemir scripts for 2020-2024 show a decrease in scripts over 5 years (2020: 35,335 to 2024: 27,987; Services Australia PBS Item Reports Online).
Estimated annual script growth	1.6% per year	Assumed.	This assumption was not reasonable as it is inconsistent with the declining numbers of insulin detemir scripts from 2020 to 2024. Insulin glargine script numbers have also been declining over the same time period.
Estimated use of insulin degludec	100% uptake from insulin detemir scripts (if not discontinued)	It was assumed that all insulin detemir scripts will be substituted by insulin degludec; and insulin degludec will not substitute for other basal insulins (e.g. insulin glargine).	The evaluation and the ESC considered that the assumption that all insulin detemir patients will switch to insulin degludec was not reasonable, as some patients may switch to other basal insulins (e.g. insulin glargine). The evaluation and the ESC considered that the assumption that insulin degludec will only substitute insulin detemir scripts was not reasonable, given the resubmission noted expert opinion that there is an unmet clinical need for insulin degludec in some patients and insulin degludec may replace insulin glargine or other basal insulins (p14, of the resubmission). In addition, insulin degludec may replace insulin detemir prior to the intended removal of insulin detemir from the Australian market at the end of 2026. The PBAC considered that an uptake rate of approximately 80% was more reasonable.

Source: p95 of the resubmission; Section 4 Workbook (Tresiba).xlsm, attached to the resubmission.

6.60 Table 11 presents the estimated utilisation and financial impact of listing insulin degludec on the PBS/RPBS for the treatment of T1D.

Table 11: Estimated use and financial implications based on the proposed effective price of insulin degludec

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of insulin degludec 100 IU/mL						
Cost to PBS/RPBS less copayments (effective DMPQ $[redacted])	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Cost to PBS/RPBS less copayments (effective DPMQ $[redacted])[b]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for insulin detemir 100 IU/mL (substituted by insulin glargine 100 IU/mL)						
Cost to PBS/RPBS less copayments	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]	-$[redacted][2]
Net financial implications						
Net cost to PBS/RPBS (effective DMPQ $[redacted])	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to PBS/RPBS (effective DPMQ $[redacted])[b]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Table 4-3, p97, Table 4-4, p98, and Table 4-5, p99 of the resubmission; 'Section 4 Workbook (Tresiba)' presented with the resubmission.

Abbreviations: DPMQ, dispensed price for maximum quantity; EMP, ex-manufacturer price

[a] The 1.6% annual growth rate in scripts was not applied to insulin detemir scripts between 2025 and 2026 (Year 1).

[b] The effective DPMQ proposed in the resubmission included markups calculated based on an EMP of $[redacted] (calculated from the published DPMQ) and was recalculated during the evaluation based on the insulin degludec effective dispensed maximum quantity EMP of $[redacted].

The redacted values correspond to the following ranges:

[1] 30,000 to < 40,000

[2] $0 to < $10 million

6.61 The resubmission estimated a net cost to the PBS/RPBS of listing insulin degludec of $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total cost of $0 to < $10 million over the first 6 years of listing.

6.62 After recalculating the effective DPMQ of insulin degludec based on the proposed effective EMP using standard methods, the estimated net cost to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total cost of $0 to < $10 million over the first 6 years of listing.

6.63 During the evaluation, a sensitivity analysis was conducted with cost offsets based on using the effective price of insulin detemir (effective DPMQ $[redacted]) rather than assuming insulin detemir is substituted by insulin glargine 100 IU/mL. Based on the sensitivity analysis and using the recalculated effective DPMQ of $[redacted] for insulin degludec, the estimated net cost to the PBS/RPBS was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, a total cost of $$0 to < $10 million over the first 6 years of listing.

6.64 The estimated utilisation and financial impact of listing insulin degludec on the PBS/RPBS for the treatment of T1D was highly uncertain for the following reasons:

- The use of a single calendar year estimate of insulin detemir PBS scripts was not reasonable. Over the past 5 years the numbers of insulin detemir PBS scripts

declined from 35,335 scripts in 2020, to 27,987 in 2024. The subsequent application of 1.6% annual growth in scripts was not supported.

- The evaluation and the ESC considered that the assumption that 100% of patients who would otherwise have been treated with insulin detemir in the first 6 years of listing would switch to insulin degludec was not reasonable, as some patients may switch to other PBS-listed basal insulins (e.g. insulin glargine 100 IU/mL, insulin glargine 300 IU/mL, insulin degludec 100 IU/mL with insulin aspart). The PSCR acknowledged that it is possible that patients who would otherwise have been treated with insulin detemir will switch to an alternative insulin product or dosing regimen (e.g. continuous subcutaneous insulin infusion) and that others may substitute insulin degludec for other basal insulins or dosing regimens such as insulin glargine. The ESC advised that the proportion of patients who would switch to insulin degludec should be reconsidered, since the assumption that the switch rate would be 100% was unreasonable.
- The assumption that insulin degludec would only substitute insulin detemir scripts was not reasonable. The resubmission and the PSCR acknowledged that insulin degludec may also replace insulin glargine or insulin degludec/aspart.
- There is risk of use of insulin degludec outside of the requested restriction, among patients with T2D.

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

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule Restricted Benefit listing of insulin degludec for the treatment of type 1 diabetes mellitus (T1D). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of insulin degludec would be acceptable at the price proposed in the resubmission. The PBAC advised that the small, proposed price difference relative to insulin glargine 100 IU/mL was reasonable. However, the PBAC did not accept the cost-consequences approach in the resubmission as a basis for a price advantage. Rather, the PBAC expected that insulin degludec would offer a practical and clinical benefit for some patients, in the absence of insulin detemir being available on the PBS. Moreover, the PBAC considered that a cost-minimisation approach (CMA), although with uncertain equi-effective doses and uncertain substitution from insulin glargine 100 IU/mL and 300 IU/mL, would plausibly result in a similarly cost-effective price as proposed by the resubmission. The PBAC considered that this uncertainty was acceptable in view of: the high clinical need for an alternative to insulin detemir as described in the consumer comments; the unlikelihood of any further forthcoming trial evidence; and the estimated modest overall financial impact to the PBS.

7.2 The PBAC noted that insulin detemir is scheduled for discontinuation from the Australian market towards the end of 2026 and that the consumer comments received on this submission stated that people living with T1D value having a choice of insulin treatments. The PBAC noted that not all patients do well on insulin glargine and that some patients living with T1D have issues with nocturnal hypoglycaemia. The PBAC considered that it is important for patients (in conjunction with their clinicians) to have a choice of insulin treatments available.

7.3 The PBAC considered that whilst there is a risk of use outside of the restriction in patients who do not have T1D, that a Restricted Benefit listing would be appropriate for insulin degludec, noting that this is consistent with the current insulin detemir listings.

7.4 The PBAC noted that the resubmission proposed insulin glargine 100 IU/mL as the main comparator. The PBAC accepted this, however, noted that the pharmacokinetic profile of insulin degludec was most similar to insulin glargine 300 IU/mL. In line with advice from the ESC, the PBAC considered that insulin glargine 300 IU/mL would be an alternative comparator, noting that insulin glargine 100 IU/mL and 300 IU/mL are not interchangeable. The PBAC noted the sponsor's advice that "any crossover period during which insulin degludec and insulin detemir were both PBS listed would be short and transitional in nature", and considered it reasonable to exclude insulin detemir as a comparator on this basis and also since some patients may reasonably be expected to transition to insulin glargine before insulin detemir delists. However, the PBAC advised that if any crossover period was protracted, then the rationale for excluding insulin detemir as a relevant comparator was not well justified.

7.5 The PBAC noted that the resubmission presented data from two randomised head-to-head trials Study 3583 and Study 3770, which were previously considered by the PBAC in March 2013, as well as additional data from the three randomised trials Study 1835, Study 3995 and HypoDeg, 2 network meta-analyses and supportive data summaries in selected patient groups from an additional 11 studies.

7.6 In line with its recommendation from the March 2013 PBAC meeting (section 9, insulin degludec PSD, March 2013 PBAC meeting) and based on the data presented, the PBAC considered that insulin degludec was at least non-inferior in terms of comparative effectiveness to insulin glargine 100 IU/mL. The PBAC also considered that insulin degludec had at least non-inferior safety relative to insulin glargine 100 IU/mL. The PBAC had not considered evidence that would suggest insulin degludec would not also be at least non-inferior in effectiveness and safety when compared to insulin glargine 300 IU/mL.

7.7 The PBAC specifically noted that patients treated with insulin degludec had lower rates of confirmed nocturnal hypoglycaemia than patients treated with insulin glargine 100 IU/mL (as detailed in Table 6), and considered that increased use of continuous

glucose monitoring has not meant that these episodes will not occur, but has assisted in documenting their occurrence so that further episodes can be reduced and/or managed more effectively.

7.8 The PBAC noted the claimed potentially important clinical advantages for some patients (see paragraph 6.54) and agreed with the expert advice in the PSCR and pre-PBAC response that there may be practical advantages of this therapy over alternative insulin preparations for some patients with T1D. However, the PBAC noted that the use of a cost-consequence analysis was not adequately justified (see paragraph 0) and it did not accept this was a reasonable approach. Nonetheless, the PBAC advised that insulin degludec would be cost-effective at the price proposed in the resubmission. The PBAC reached this conclusion in view of the expected clinical advantages for some patients in the absence of insulin detemir and in view of a scenario in which a CMA compared with insulin glargine 100 IU/mL and 300 IU/mL could plausibly be expected to result in a comparable price.

7.9 Whilst heterogeneity between trials made the determination of equi-effective doses uncertain, the Committee noted the equi-effective doses proposed by the sponsor, with these being:

1 unit of insulin degludec (100 IU/mL) is equivalent to 1.16 units of insulin glargine (100 IU/mL); and

1 unit of insulin degludec (100 IU/mL) is equivalent to 1.21 units of insulin glargine (300 IU/mL) in patients who are switching from insulin detemir.

7.10 The PBAC noted that based on the proposed equi-effective doses, a CMA compared to insulin glargine 100 IU/mL would result in a higher price compared to that proposed in the resubmission. However, as noted above, the PBAC considered that insulin glargine 300 IU/mL was an alternative comparator, and it advised that some patients would switch from insulin detemir to insulin glargine 300 IU/mL. Given the dose relativities previously accepted to inform the pricing of insulin glargine 300 IU/mL (1 unit 300 IU/mL being equi-effective to 0.84 units of insulin glargine 100 IU/mL, see para 5.4), the PBAC considered the a CMA with a mixed comparator of insulin glargine 100 IU/mL and 300 IU/mL would likely result in a price reasonably comparable to that proposed in the resubmission.

7.11 With respect to the financial estimates presented by the resubmission, the PBAC considered that uptake from patients switching from insulin detemir would be lower than 100% (more likely to be in the range of 80%), with some patients switching to insulin glargine. The PBAC also considered that some patients using insulin glargine would want to try something new and therefore be switched to insulin degludec. Overall, the PBAC considered the estimated cost of $0 to < $10 million over 6 years for approximately 10,000 to < 20,000 patients per annum (based on approximately

30,000 to < 40,000 scripts) may be an overestimate, particularly as more people transition to insulin pumps which only use quick acting insulin.

7.12 The PBAC advised that insulin degludec is suitable for prescribing by nurse practitioners.

7.13 The PBAC recommended that the Early Supply Rule should apply.

7.14 The PBAC recommended that insulin degludec should not be treated as interchangeable on an individual patient basis with any other drugs.

7.15 The PBAC noted that because insulin degludec is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over insulin glargine, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.16 The PBAC noted that this resubmission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
INSULIN DEGLUDEC						
Insulin degludec 100 units/mL injection, 5 x 3 mL cartridges		NEW MP NP	5	5	1	Tresiba
Restriction Summary [new1] / Treatment of Concept: [new1A]						
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners					
	Restriction type: ☒Restricted benefit					
Prescribing rule level	**Administrative Advice:** Special Pricing Arrangements apply.					
	Episodicity: [blank]					
	Severity: [blank]					
	Condition: Type 1 diabetes					
	Indication: Type 1 diabetes					
	Treatment Phase: [blank]					

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Novo Nordisk is pleased that the PBAC has agreed to the listing of Tresiba® (insulin degludec) 100 IU/mL for the treatment of Type 1 diabetes mellitus (T1DM). This will provide another important and valuable option for patients living with T1DM.