5.09 INSULIN DEGLUDEC WITH INSULIN ASPART, Injections, cartridges, 70 units-30 units per mL, 3 mL, 5
Injections, pre-filled pen, 70 units-30 units per mL, 3 mL, 5
Ryzodeg®, Novo Nordisk Pharmaceuticals Pty Ltd

1 Purpose of application

1.1 The submission requested an unrestricted listing for insulin degludec with insulin aspart (IDegAsp) for treatment of adult patients with diabetes mellitus where insulin treatment is necessary.

1.2 For the proposed drug a cost-minimisation was made to biphasic insulin aspart 30 (BIAsp 30) as main comparator in type 2 diabetes mellitus (T2DM) patients and insulin detemir (IDet) in type 1 diabetes mellitus (T1DM) patients.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Diabetes mellitus
Intervention	Co-formulated 70% IDeg (basal/long-acting) + 30% IAsp (bolus/bolus-acting) Dosed once-daily or twice-daily with the main meal(s)
Comparator	T2DM: 30% IAsp and 70% protamine-crystallised IAsp (BIAsp 30) T1DM: IDet
Outcomes	Noninferior HbA1c Lower fasting plasma glucose Lower risk of hypoglycaemia Lower total insulin dose
Clinical claim	T2DM: IDegAsp is noninferior in terms of effectiveness (change in HbA1c) and superior in terms of safety (confirmed hypoglycaemia) compared with BIAsp 30. T1DM: IDegAsp is noninferior in terms of effectiveness (change in HbA1c) and superior in terms of safety (confirmed nocturnal hypoglycaemia) compared with IDet.

Source: Table 1.1.1, p13 of the submission

BIAsp = biphasic insulin aspart; HbA1c = glycated haemoglobin; IAsp = insulin aspart; IDeg insulin degludec; IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

2 Requested listing

Name, restriction, manner of administration, form	Max Qty (packs)	Max Qty (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
INSULIN DEGLUDEC + INSULIN ASPART insulin degludec 70 units/mL + insulin aspart 30 units/mL injection, 5 x 3 mL syringes	5	5	1	**Published** $[redacted] **Effective** SPA $[redacted]	Ryzodeg® FlexTouch® & Ryzodeg® Penfill®[b], Novo Nordisk Pharmaceuticals Pty Limited

Condition	Type 1 diabetes mellitus and type 2 diabetes mellitus
PBS Indication	To improve glycaemic control in adults with diabetes mellitus requiring basal and prandial insulin (where insulin treatment is necessary)
Population criteria	Adults with diabetes mellitus (age ≥ 18 years)
Restriction:	Unrestricted

SPA = special price arrangement

2.1 The submission proposed a special price arrangement (SPA) with an effective dispensed price of $[redacted]. The requested published dispensed price is $[redacted].

3 Background

Registration status

3.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. The second round clinical evaluation report and TGA Delegate's Overview were available to the PBAC. TGA approval is expected in mid-November 2017. The PBAC noted that IDeg as a single agent is currently undergoing TGA evaluation (submission, p18).

3.2 IDegAsp has not been considered previously by the PBAC.

Previous PBAC considerations of insulin products

3.3 There is a range of insulin products currently subsidised on the PBS. Many have been listed for a considerable time. Insulin NPH (human) was PBS listed in 1986, insulin lispro was listed in 1996. The therapeutic relativity sheets and Public Summary Documents (PSDs) provide the following information in relation to previous PBAC recommendations for insulin products:

- Insulin lispro was accepted for listing on the basis of an advantage over short acting insulin (this is reflected in a price premium of 20% over NPH);
- The insulin lispro-insulin lispro protamine combination insulin product was listed on the basis that it deserves a premium similar to that for plain insulin lispro compared to regular human insulin (this is reflected in a price premium of 20% over NPH);
- Insulin aspart and Insulin glulisine were recommended on a cost-minimisation basis to insulin lispro (unit to unit);

- Insulin glargine was recommended for listing on a cost-effectiveness basis versus insulin NPH (this is reflected in a price premium of [redacted]% over NPH)
- Insulin detemir was recommended for listing on a cost minimisation basis with insulin glargine for T1DM (unit to unit);
- Insulin detemir was recommended for listing for use in T2DM on a cost-minimisation basis with insulin glargine. However, the PBAC had doubts regarding the equi-effective dose of detemir versus glargine. The submission claimed that one unit of detemir was equivalent to one unit of glargine, based on the direct randomised controlled data. When the calculations were adjusted to allow for the disparate dosing of detemir and glargine in the clinical trials, the analysis suggested a daily per unit ratio of 1.10 of detemir to glargine. The sponsor elected not to proceed with this listing; and
- Insulin glargine and insulin detemir have special pricing arrangements.

Table 2: Ex-manufacturer prices (AEMP) of currently listed insulin products and proposed new product

Legal Instrument Drug	Legal Instrument Form	Brand Name	Pack Quantity	AEMP	Price per unit of insulin
Insulin degludec + insulin aspart	insulin degludec 70 units/mL + insulin aspart 30 units/mL injection, 5 x 3 mL syringes		1	Proposed $[redacted]	[redacted]
Insulin detemir	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	Levemir FlexPen Levemir Penfill	1	$[redacted]*	[redacted]
Insulin glargine	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	Lantus	1	$[redacted]*	[redacted]
Insulin aspart	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	NovoRapid FlexPen NovoRapid Penfill 3 mL	1	$42.38	0.02825
Insulin aspart with insulin aspart protamine suspension	Injections (human analogue), cartridges, 30 units-70 units per mL, 3 mL, 5	NovoMix 30 FlexPen NovoMix 30 Penfill 3 mL	1	$42.38	0.02825
Insulin glulisine	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	Apidra Apidra SoloStar	1	$42.38	0.02825
Insulin lispro	Injections (human analogue), cartridges, 100 units per mL, 3 mL, 5	Humalog Humalog KwikPen	1	$42.38	0.02825
Insulin lispro with insulin lispro protamine suspension	Injections (human analogue), cartridges, 25 units-75 units per mL, 3 mL, 5	Humalog Mix25 Humalog Mix25 KwikPen	1	$42.38	0.02825
Insulin lispro with insulin lispro protamine suspension	Injections (human analogue), cartridges, 50 units-50 units per mL, 3 mL, 5	Humalog Mix50 Humalog Mix50 KwikPen	1	$42.38	0.02825
Insulin isophane	Injections (human), cartridges, 100 units per mL, 3 mL, 5	Humulin NPH Protaphane InnoLet Protaphane Penfill 3 mL	1	$35.32	0.02355
Insulin neutral	Injections (human), cartridges, 100 units per mL, 3 mL, 5	Actrapid Penfill 3 mL Humulin R	1	$35.32	0.02355
Insulin neutral with insulin isophane	Injections (human), cartridges, 30 units-70 units per mL, 3 mL, 5	Humulin 30/70 Mixtard 30/70 InnoLet	1	$35.32	0.02355
Insulin neutral with insulin isophane	Injections (human), cartridges, 30 units-70 units per mL, 3 mL, 5	Mixtard 30/70 Penfill 3 mL Mixtard 50/50 Penfill 3 mL	1	$35.32	0.02355

Source: compiled during evaluation
NPH = neutral protamine Hagedorn
*Effective price

4 Population and disease

4.1 IDegAsp is a premixed insulin that the submission proposed will be used for the treatment of adults with T1DM and T2DM in order to achieve good glycaemic control without increasing the risk of adverse events (AE) such as hypoglycaemic events. Premixed insulins are especially used in T2DM patients for glycaemic control

as they cover the basal needs through the day and the bolus needs for meal times. The existing premixed insulins are typically a 70/30 mixture of an intermediate-acting and a fast-acting insulin. However, due to physiological incompatibilities it was not possible, until recently, to combine long- and short-acting insulins. If listed IDegAsp would be the first long acting/short acting premixed insulin available on the PBS.

4.2 The clinical management algorithms for T2DM patients are based on a position statement of the Australian Diabetes Society (Gunton et al 2016). This treatment algorithm for T2DM consists of first line, second line and third line treatment. The proposed drug would be similarly positioned as other premixed insulins which include mixtures of basal and bolus insulins. Insulin treatment is used typically as a second or third line treatment.

4.3 The submission did not present clinical management for T1DM. Insulin is a necessary therapy for patients with T1DM. Typically, a combination of a long-acting and a short-acting insulin is used for these patients. Premixed insulins are also used as part of the treatment regimen for T1DM patients; however, they play only a very minor role in managing T1DM patients. The dosage of insulin for these patients is adjusted to the frequency of meal(s) and carbohydrate intake.

4.4 The PBAC accepted the clinical place of IDegAsp in T2DM as proposed by the submission but considered that the clinical place of IDegAsp in T1DM was unclear as pre-mixed insulins are generally not preferred in this population.

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

5 Comparator

T2DM

5.1 The submission nominated BIAsp 30, a premixed insulin, as the main comparator in T2DM patients. The main arguments provided in support of this nomination are the pharmacologic similarities of both drugs and that both formulations are premixed insulins. BIAsp 30 holds a market share of 70% of the PBS premixed insulin market.

5.2 The PBAC considered that BIAsp30 was an appropriate comparator for T2DM.

5.3 The PBAC could only recommend listing of IDegAsp if it is satisfied that IDegAsp provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies The PBAC noted it had previously accepted there was a clinical advantage to using insulin aspart over short acting insulins (through insulin lispro). The PBAC was satisfied that IDegAsp would provide a similar clinical advantage over short acting insulins.

5.4 The PBAC did not consider insulin glargine (IGlar) to be an alternative therapy to IDegAsp for T2DM. The PBAC agreed with the pre-PBAC response (p1) that basal bolus use incorporating IGlar is not expected to change with the introduction of IDegAsp and that IGlar is targeted to a different patient population from IDegAsp. However, the PBAC noted that the price requested for IDegAsp was higher than that

for IGlar and that a clinical comparison against IGlar in T2DM may be informative in this context.

T1DM

5.5 The submission nominated insulin detemir (IDet) as the main comparator in T1DM patients.

5.6 The PBAC noted that pre-mixed insulins are not typically used in T1DM and considered that it was not clear what role IDegAsp would have in T1DM if listed. The PBAC considered that although there may be a small uptake in T1DM patients currently using a pre-mixed insulin who may switch to IDegAsp, it would be unlikely that prescribers would substitute IDegAsp for basal plus bolus treatments.

5.7 The PBAC considered that the comparator proposed for the T2DM population (BIAsp 30) or other premixed insulins may be more appropriate comparators for T1DM as they possess pharmacologic similarities and both formulations are premixed insulins.

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 detailed his personal experience treating diabetic patients and discussed the importance of hypoglycaemic control. The clinician stated that IDegAsp had demonstrated significant reductions in the risk of confirmed hypoglycaemia in clinical trials. The clinician described that the fear of future episodes of hypoglycaemia conflicts with treatment success, for both patients and clinicians. Patients may self-modify their insulin doses following a hypoglycaemic event, which in turn may impact the proper treatment of their condition. The clinician considered that IDegAsp, the first combination of basal and ultra, long-acting insulin, may increase the chances that patients will meet targets for HbA1c and would likely be the pre-mixed insulin of choice for T2DM patients.

6.2 The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

Consumer comments

6.3 The PBAC noted and welcomed the input from one organisation, the Australian Diabetes Society, via the Consumer Comments facility on the PBS website. The Australian Diabetes Society supported the use of IDegAsp in clinical practice. The PBAC noted the advice that recent studies have shown that the use of IDegAsp has been shown to reduce the risk of hypoglycaemia in both T1DM and T2DM, particularly nocturnal hypoglycaemic events and that IDegAsp and IGlar achieved similar HbA1c reduction. The Australian Diabetes Society also noted that IDegAsp would be the first available combination of rapid and ultralong-acting insulin. The PBAC noted that this advice was supportive of the submission.

Clinical trials

6.4 The submission was based on three head-to-head trials comparing IDegAsp to BIAsp 30 (study 3940, N=394; study 3592, N=447; study 3597, N=424) for T2DM patients and one head-to-head trial (main trial with extension trial) comparing IDegAsp to IDet (study 3594/3645, N=548) for T1DM patients. No subgroup analyses or meta-analyses were required. The T2DM trials were not pooled in the clinical evidence as they were from three different population groups; 3940 (T2DM, insulin-naïve), 3592 (T2DM, insulin-experienced), and 3597 (T2DM, insulin-experienced, Japanese study). A supplementary pooled analysis of 3592, and 3597 was provided.

6.5 Details of the trials presented in the submission for T2DM are provided in table 3.

Table 3: Trials and associated reports presented in the submission for T2DM

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
3940 (T2DM, insulin-naïve)	A 26-week, randomised, open-label, multinational treat-to-target trial comparing efficacy and safety of IDegAsp BID and BIAsp 30 BID both with metformin in insulin naïve subjects with type 2 diabetes mellitus inadequately controlled on metformin monotherapy or metformin in combination with one OAD. Franek, E., et al. (2016). Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naïve adults with Type 2 diabetes.	June 2013 Diabetic Medicine 33(4): 497-505.
3592 (T2DM, insulin-experienced)	A 26-week, randomised, open-labelled, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of NN5401 twice daily (BID) with biphasic insulin aspart (BIAsp) 30 BID, with or without metformin, with or without DPP-4 inhibitor, with or without pioglitazone in subjects with type 2 diabetes in inadequate glycaemic control on once or twice daily premixed or self-mixed insulin regimen with or without OADs. Fulcher, G. R., et al. (2014). Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: A phase 3a, randomized, treat-to-target trial.	May 2011 Diabetes Care 37(8): 2084-2090.
3597 (T2DM, insulin-experienced)	A 26-week trial, randomised, open-label, two-arm, parallel-group, treat-to-target study comparing efficacy and safety of the NN5401 twice daily with biphasic insulin aspart 30 twice daily, with or without metformin in subjects with type 2 diabetes in inadequate glycaemic control on once or twice daily insulin regimen with or without metformin. Christiansen, J. S., et al. (2013). Superior FPG control and less nocturnal hypoglycaemia with IDegAsp vs BIAsp 30 in Asian subjects poorly controlled on basal or pre/self-mixed insulin: Randomised phase 3 trial	June 2011 Diabetologia 56: S420.

Source: Table 2.2.2, p27 of the submission
BIAsp 30 = biphasic insulin aspart; BID = twice-daily; DPP-4i = dipeptidyl peptidase 4 inhibitor; FPG = fasting plasma glucose IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; OAD = oral antidiabetic drug; T2DM = type 2 diabetes mellitus

6.6 Details of the trials presented in the submission for T1DM are provided in the table 4.

Table 4: Trials and associated reports presented in the submission for T1DM

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
3594 (main trial, T1DM) 3645 (extension trial, T1DM)	An extension trial comparing safety and efficacy of NN5401 plus meal-time insulin aspart for the remaining meals with IDet plus meal-time insulin aspart in type 1 diabetes. A 26 week, multinational, multi-centre, open labelled, two arm, parallel, randomised, treat to target trial comparing efficacy and safety of NN5401 once daily plus meal time insulin aspart for the remaining meals vs. basal bolus treatment with IDet plus meal time insulin aspart in subjects with type 1 diabetes. Hirsch, I. B., et al. (2017). Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal–bolus treatment in people with Type 1 diabetes: 1–year results from a randomized clinical trial (BOOST® T1). Hirsch, I. B., et al. (2012). Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: A 26-week, phase 3, randomized, open-label, treat-to-target trial.	November 2010 June 2011 Diabetes Care 35(11): 2174-2181. Diabetic Medicine 34(2): 167-173.

Source: Table 2.2.2, p27 of the submission; compiled during evaluation
IDet = insulin detemir; T1DM = type 1 diabetes mellitus

6.7 The key features of the direct randomised trials are summarised in the table 5.

Table 5: Key features of the included evidence, IDegAsp vs. BIASp30 (T2DM) and IDegAsp vs. IDet (T1DM)

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in CMA
3940	394	R, OL 26 weeks	low/unclear	T2DM, insulin-naïve	HbA1c hypoglycaemic events FPG insulin dose	hypoglycaemic events insulin dose
3592	447	R, OL 26 weeks	low/unclear	T2DM, insulin-experienced		
3597	424	R, OL 26 weeks	low/unclear	T2DM, insulin-experienced		
3594	548	R, OL 26 weeks	low/unclear	T1DM, main trial		
3645	548	R, OL 26 weeks	low/unclear	T1DM, extension trial		

Source: Table 2.3.1, p29 of the submission compiled during the evaluation
BIAsp 30 = biphasic insulin aspart; IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir;
FPG = fasting plasma glucose; HbA1c = glycated haemoglobin; OL = open label; R = randomised; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; CMA = cost-minimisation analysis

6.8 The ESC and PBAC noted the risk of bias in these open label trials and considered that this risk was in part mitigated by the use of objective outcome measures such as HbA1c. However, the PBAC agreed with the ESC that it was difficult to assess the likely impact of IDegAsp on overall rates of hypoglycaemia in clinical practice on the

basis of these trials, particularly asymptomatic hypoglycaemia, as there would be less testing in the clinical environment than in a study environment.

6.9 The PBAC further considered that the comparison against IDet in T1DM was of limited value for decision making, as this drug is unlikely to be replaced in clinical practice in this population.

Comparative effectiveness

6.10 The results for the primary outcome (change in HbA1c) of the direct randomised trials are summarised in the table 6.

Table 6: Results of change in HbA1c (%) from baseline across the studies

	IDegAsp mean change from baseline (SE)	Comparator mean change from baseline (SE)	Mean difference (95% CI)
Trial ID 3940 – T2DM (insulin-naïve), 26 weeks			
IDegAsp BID N = 197; BIAsp 30 N = 197	-1.71 (0.10)	-1.73 (0.09)	0.02 (-0.12, 0.17)
Trial ID 3592 – T2DM (insulin-experienced), 26 weeks			
IDegAsp BID N = 224; BIAsp 30 N = 222	-1.31 (0.09)	-1.29 (0.10)	-0.03 (-0.18, 0.13)
Trial ID 3597 – T2DM (insulin-experienced), 26 weeks			
IDegAsp BID N = 280; BIAsp 30 N = 142	-1.39 (0.05)	-1.44 (0.07)	0.05 (-0.10, 0.20)
Trial ID 3594 – T1DM (main study), 26 weeks			
IDegAsp N = 366; IDet N = 182	-0.75 (0.06)	-0.70 (0.08)	-0.05 (-0.18, 0.08)
Trial ID 3645 – T1DM (extension study), 52 weeks			
IDegAsp N = 366; IDet N = 182	-0.67 (0.07)	-0.57 (0.08)	-0.10 (-0.24, 0.03)

Source: Table 2.5.1 p46 of the submission

BIAsp 30 = biphasic insulin aspart; BID = twice-daily; CI = confidence interval; IDegAsp = insulin degludec/insulin aspart; N = number of subjects contributing to the analysis; SE = standard error of the mean; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

6.11 The results of the four trials, excluding the extension trial (study 3645), were in agreement with the predetermined non-inferiority margin proposed. The proposed drug was non-inferior for all the analysed trials with a non-inferiority margin of 0.4%. None of the trials showed superiority for change in HbA1c.

Comparative harms

6.12 The adverse event profiles of the proposed drug and the submission nominated comparators were similar with no statistical differences in all adverse events, adverse events resulting in withdrawal, serious adverse events, and mortality.

6.13 Trials 3940, 3592, 3597, and 3594/3645 collected hypoglycaemic episodes recorded by subjects in their trial diaries throughout the trial. Information to be collected included plasma glucose (PG) before treating the episode and whether the subject was able to treat him/herself. Hypoglycaemic episodes were reported at all visits. If the subject reported one or more hypoglycaemic episodes (symptomatic or asymptomatic) since the last visit or phone contact, the investigator or trial coordinator completed a hypoglycaemia questionnaire/interview. Confirmed

episodes included severe episodes (subject not able to treat him/herself) plus minor episodes (symptoms consistent with hypoglycaemia with confirmation by PG <3.1 mmol/L (56 mg/dL) or full blood glucose <2.8 mmol/L (50 mg/dL) and handled by the subject him/herself; or any asymptomatic PG value <3.1 mmol/L (56 mg/dL) or full blood glucose value <2.8 mmol/L (50 mg/dL). The nocturnal period was defined as 00:01 to 05:59 inclusive (Source: Table 2.4.2, p33 of Commentary, Table 2.4.9, p44 of the submission).

6.14 There were less confirmed hypoglycaemic events (treatment ratio) in the proposed drug IDegAsp compared to BIAsp 30 in studies 3940 and 3592 and less nocturnal hypoglycaemic events in IDegAsp compared to IDet in study 3645 (Table 7); however, there was no difference in confirmed hypoglycaemic events for IDegAsp compared to BIAsp 30 in study 3597.

6.15 There was no difference between IDegAsp and the submission nominated comparator drugs in the relative risk of an individual person experiencing one or more confirmed or severe hypoglycaemia events in the four trials. Similarly, there was no difference in the total numbers of severe hypoglycaemic events between the proposed drug IDegAsp and the comparator drugs in the four trials.

6.16 The Pre-Sub Committee Response (PSCR) argued (p2) that the hypoglycaemia rate or 'treatment ratio' (incidence rate ratio) "based on the event rate per 100 patient-years of exposure (PYE) is an appropriate calculation … which accounts for all confirmed hypoglycaemic events, rather than one event per patient".

6.17 The PBAC noted that there were differences in the total documented hypoglycaemic events per 100 PYE in some but not all trials, and considered that the clinical significance of these differences is uncertain particularly as some of the events were asymptomatic and there were no significant differences in severe hypoglycaemic events per 100 PYE.

Table 7: Results of analysis of confirmed and severe hypoglycaemias across the studies

Trial ID	Proposed medicine	Main comparator	Treatment ratio (95% CI)
	No. of Events (per 100 PYE)	No. of Events (per 100 PYE)	
3940 – T2DM, insulin-naïve, 26 weeks			
Confirmed hypo	553 (580)	1221 (1301)	**0.46 (0.35, 0.61)**
Severe hypo	5 (5)	3 (3)	NR
3592 – T2DM, insulin-experienced, 26 weeks			
Confirmed hypo	993 (972)	1379 (1396)	**0.68 (0.52, 0.89)**
Severe hypo	9(9)	25(25)	NR
3597 – T2DM, insulin-experienced (Asian study), 26 weeks			
Confirmed hypo	1227 (956)	621 (952)	1.00 (0.76, 1.32)
Severe hypo	6(5)	2(3)	NR
3594 – T1DM (main study), 26 weeks			
Confirmed hypo	6634 (3917)	3720 (4434)	NR
Severe hypo	56(33)	35(42)	NR
3645 – T1DM (extension study), 52 weeks			
Confirmed hypo	9450 (3183)	5342 (3673)	NR
Severe hypo	79(22)	65(45)	NR

Source: Table 2.5.6 of the Commentary, Tables 2.5.10, p52 of the submission; CSR Study 3594, Tables 12-18 to 12-19, p140 and p143; CSR Study 3645, Table 12-20 to 12-21; CSR Study; 3940, Tables 12-14 to 12-15; CSR Study 3592, Tables 12-14 to 12-15; CSR Study 3597, Tables 12-13 to 12-14, Values for severe hypos were compiled during evaluation.
CI = confidence interval; N = total participants in group; NR = not reported; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; PYE = patient years of exposure
Bold = statistically significant

6.18 Additionally, the PBAC noted that blood glucose levels in the studies were measured using self-measuring devices rather than continuous blood glucose monitoring and therefore do not provide complete or accurate data of blood glucose levels over the whole dosing interval.

Benefits and harms

6.19 As the PBAC did not accept the submission's claim of superior safety, a benefit and harms table has not been presented.

Interpretation of clinical evidence

6.20 The submission concluded that in T2DM and T1DM patients IDegAsp had non-inferior effectiveness (measured by the change in HBA1c). The PBAC considered this claim to be reasonably supported for T2DM. As noted above, the PBAC considered the comparison against IDet in T1DM to be of limited usefulness for decision making.

6.21 The submission concluded that in T2DM and T1DM patients IDegAsp had superior safety in terms of rate of confirmed hypoglycaemic events. The evaluation and ESC considered this claim was not well supported by the evidence as IDegAsp was non-inferior:

- in study 3597 (T2DM, insulin-experienced (Asian study)) in the rate of confirmed hypoglycaemic events;
- in terms of risk of a patient experiencing one or more confirmed hypoglycaemic events or confirmed severe hypoglycaemic events; and
- in terms of rates of confirmed severe hypoglycaemic events.

6.22 The PSCR (p2) claimed that IDegAsp provided a clinically meaningful reduction in the treatment ratio of confirmed and nocturnal hypoglycaemia to support the superior safety of IDegAsp over the comparators. In particular, based on the American Diabetes Association (ADA) work group on hypoglycaemia, a reduction in rate of confirmed and nocturnal hypoglycaemia of ≥30% by a new drug is considered clinically meaningful. Further, the PSCR claimed that for hypoglycaemic episodes, including less severe hypoglycaemic episodes (confirmed and nocturnal hypoglycaemia) often precede severe hypoglycaemia and are considered the greatest risk factor for the development of severe hypoglycaemia in the future which were not demonstrated in trials specifically for IDegAsp. The PSCR also claimed that non-severe hypoglycaemia will have an impact on cardiovascular deaths and overall survival. The pre-PBAC response (p2) argued that these trials were not designed to measure outcomes of hypoglycaemia but that the link between hypoglycaemia and these long-term conditions has been well established.

6.23 The PBAC considered that while IDegAsp was statistically superior in terms of number of biochemically confirmed hypoglycaemic episodes in some trials, this difference may not be clinically meaningful, particularly as there was no difference in the relative risk of an individual patient having at least one confirmed hypoglycaemic event and there was no difference in the risk of a patient having a severe hypoglycaemic event (either relative risk or incidence rate ratios). Thus the PBAC did not accept the submission's claim of superior safety.

Economic analysis

6.24 The submission presented a cost-minimisation analysis of IDegAsp versus BIAsp 30 (T2DM) and IDet (T1DM), with cost offsets for severe hypoglycaemic events. The PBAC noted the submission's approach was in line with the clinical evidence of non-inferior efficacy in T2DM, but not in line with the clinical evidence for safety.

6.25 The submission did not take a conventional approach of calculating the cost minimised price of the drug based on equi-effective doses and cost offsets; rather, the submission set the price of IDegAsp at an effective DMPQ of $[redacted] and calculated that at this price the listing of IDegAsp would be overall cost-saving due to differences in the rates of hypoglycaemic events.

6.26 Table 8 presents the components of the submission's cost-minimisation approach.

Table 8: Key assumptions and components of the cost-minimisation approach

Component	Claim or assumption
Cost of comparators	<table><tr><th></th><th>DPMQ</th><th>Price per unit</th></tr><tr><td>BIAsp 30, 5 x 3 mL syringes</td><td>$240.07</td><td>$0.03</td></tr><tr><td>IDet, 5 x 3 mL syringes</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>IAsp, 5 x 3 mL syringes</td><td>$240.07</td><td>$0.03</td></tr><tr><td>IDegAsp, 5 x 3 mL syringes</td><td>[redacted]</td><td>[redacted]</td></tr></table>
Equi-effective doses	The submission used trial based data to estimate the equi-effective doses of IDegAsp compared to BIAsp 30 and IDet in different population groups. The equi-effective doses used in the submission were: 1 unit IDegAsp : 1 unit BIAsp 30 in T2DM (Insulin-naïve) 0.82 units IDegAsp : 1 unit BIAsp 30 in T2DM (Insulin-experienced) 0.81 units IDegAsp : 1 unit IDet in T1DM (Basal only)
Cost offsets	The submission used the difference in bolus insulin dose utilisation in T1DM. The submission used a difference in severe hypoglycemic event rates to cost offset service utilisation. Rather than using the number of severe hypos in each arm of the trials, the submission estimated the number of severe hypos. This was based on the mean number of severe hypos per confirmed hypoglycemic event in the total trial, multiplied by the number of confirmed hypos in each arm. Overall, this overestimated the number of severe hypos in the control arms. Average cost per severe hypoglycemic event = $2943 (See Table 9) <table><tr><td>Severe hypoglycaemia costs</td><td>Comparator</td><td>IDegAsp</td><td>Difference</td></tr><tr><td>Average cost per patient per year</td><td>$910.29</td><td>$605.20</td><td>$305.09</td></tr></table>

Source: Compiled during evaluation, and calculated during evaluation
BIAsp = biphasic insulin aspart; IAsp = insulin aspart; IDeg=insulin degludec, IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, hypos = hypoglycaemic events

Table 9 Submission's derivation of severe hypoglycaemic event cost

Resource	Patients (%)	Cost, 2009-10 prices	Average cost per event (2017-18 price[d])
Ambulance	66.6%	$738[a]	$492
Emergency department visit	65.2%	$600[b]	$391
Hospitalisation	31.8%	$5,318[c]	$1,691
Total cost			$2,574 ($2,943)

Source: Table 3.3.3, submission, p71. Notes: a Life threatening or urgent ambulance call-out. b Fremantle Hospital (Director of ED, personal communication). c Average cost of hospitalisation with hypoglycaemia as a principal diagnosis. d Inflated using Total Health Price Index (AIHW 2016)

6.27 Using this methodology, the submission estimated that there would be a cost saving of $[redacted] per patient per year with T1DM and cost neutrality for patients with T2DM.

6.28 The PSCR (pp4-5) presented a sensitivity analysis which uses the reported rates of severe hypoglycaemic events per trial arm and claimed a cost saving of $[redacted] per patient per year with T1DM and $[redacted] for patients with T2DM for a combined save of $[redacted] per patient per year.

6.29 The PBAC did not accept the approach taken by the submission which assumed a difference in severe hypoglycaemic events. Therefore, the PBAC considered that it was not appropriate for the price of IDegAsp to include a premium over BIAsp 30 in T2DM to account for a reduction in hypoglycaemic events based on the evidence provided in the submission. Additionally, the PBAC considered that the differences in biochemically confirmed hypoglycaemia were not clinically meaningful and noted that there were no statistically significant differences in the rates of severe hypoglycaemic events.

6.30 The PBAC noted the submission proposed the equi-effective doses for IDegAsp compared to BIAsp 30 in T2DM to be different for insulin-naïve (1:1) and insulin-experienced (0.82:1) patients (weighted equi-effective dose is [redacted], assuming [redacted]% insulin naïve and [redacted]% insulin experienced patients (submission table 3.1.2 p 64)). The submission postulated that this is "related to the glucose lowering profile of IDegAsp, in which the rapid acting prandial effect is followed by a distinct separate and stable basal effect" (p62). Although the ESC considered that the approach used in the submission which resulted in different equi-effective doses was reasonable, the PBAC considered that the differences in naïve and experienced patients created some uncertainty in the equi-effective dose overall.

6.31 As, the PBAC did not consider IDet to be the appropriate comparator for T1DM, the Committee did not form a view on the cost-minimisation analysis or equi-effective doses of IDegAsp in this setting.

6.32 The PBAC noted the Department's advice that prices should be calculated using approved ex-manufacturer prices and not DPMQ prices.

Drug cost/patient/year: $[redacted] at DPMQ

6.33 The submission estimated a weighted drug cost/patient/year of $[redacted] for IDegAsp. This was based on a weighted mean drug cost/patient/year of $[redacted] for insulin-experienced T2DM patients ([redacted]%), $[redacted] for insulin-naïve T2DM patients ([redacted]%), and $[redacted] for T1DM patients ([redacted]%). This was based on a DPMQ of $[redacted].

6.34 The submission estimated a weighted drug cost/patient/year of $[redacted] for the comparators. This was based on a weighted mean drug cost/patient/year of $1,008 for BIAsp 30 in insulin-experienced T2DM patients ([redacted]%), $865 for BIAsp 30 in insulin-naïve T2DM patients ([redacted]%), and $[redacted] for IDet in T1DM patients ([redacted]%) and a higher number of insulin units used per year compared to IDegAsp.

6.35 The pre-PBAC response (p1) proposed a reduced DPMQ of $[redacted], which incorporated the cost-minimised price of IDegAsp to 70%IGlar/30%IAsp, accounted in 17% premixed neutral/isophane human insulin use and assumed the effective dispensed price of IGlar to be equivalent to IDet. The PBAC considered this price reduction was not sufficient to address its concerns regarding cost-effectiveness.

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC. A market share approach was chosen using PBS and RPBS utilisation statistics for estimating the total units of premixed and long-acting insulins used in Australia in 2016.

6.37 The submission identified eight insulin formulations that were likely to be replaced.

6.38 Table 10 summarises the insulin PBS items, the expected annual growth rate and the expected replacement of these items if IDegAsp were to be listed on the PBS.

Table 10: Assumed growth rate and proportions of each of the current treatments displaced by the insulin degludec/ insulin aspart

Item	Drug	Annual growth rate	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
8609D	Insulin aspart/insulin aspart protamine	3.7%	5.0%	15.0%	25.0%	35.0%	45.0%	55.0%
8390N	Insulin lispro/insulin lispro protamine	2.6%	3.0%	10.0%	15.0%	20.0%	25.0%	30.0%
8874C	Insulin lispro/insulin lispro protamine	5.9%	3.0%	10.0%	15.0%	20.0%	25.0%	30.0%
1426C	Insulin isophane human/insulin neutral human	-14.5%	3.0%	10.0%	15.0%	20.0%	25.0%	30.0%
1763T	Insulin isophane human/insulin neutral human	-11.5%	3.0%	10.0%	15.0%	20.0%	25.0%	30.0%
2062M	Insulin isophane human/insulin neutral human	-10.7%	3.0%	10.0%	15.0%	20.0%	25.0%	30.0%
9040T	Insulin detemir	3.6%	1.0%	2.0%	3.0%	4.0%	5.0%	6.0%
9039R	Insulin glargine	6.3%	1.0%	2.0%	3.5%	5.0%	7.0%	9.0%

Source: Tables 4.3 and 4.5, p77 of the submission; compiled during evaluation

6.39 The submission applied script equivalence ratios based on those identified in the clinical evaluation; however, there was an assumption that formulations not compared in the clinical evidence would have similar equi-effectiveness to those identified in the clinical trials. The evaluation considered that this was not appropriate. The PSCR (p4) argued that the script equivalence ratios were appropriate as the IDegAsp versus BIAsp 30 equivalence ratio was based on the weighted averages for the T2DM clinical trials and IDegAsp versus IDet was based on the T1DM trial. Where established relativities were lacking (i.e., for premixed human insulins), a 1:1 equivalence ratio was used. However, the ESC noted the submission used the BIAsp 30:IDegAsp relativities from the trials for lispro premixes and the IDet:IDegAsp relativities for glargine, not the 1:1 relativities as suggested.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of eligible patients[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of IDegAsp						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for comparators**						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 4.14, p82, table 4.21, p87, table 4.22, p87 of the submission

IDegAsp = insulin degludec/insulin aspart; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Assuming 3.4 scripts per year as estimated during evaluation. ** calculated using effective prices for insulin determir and glargine.

The redacted table shows that at year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be less than $10 million per year.

6.40 Although the submission presented a cost-minimisation approach, there was an increased cost of less than $10 million to the PBS/RPBS in Year 1 rising to less than $10 million in Year 6 with a total cost increase of $20 - $30 million in the first six years of listing. This was primarily due to the inclusion of cost offsets for severe hypoglycaemias in the cost-minimisation calculations that were not included in the financial estimates.

6.41 The PBAC considered there was a high degree of uncertainty in the financial estimates as:

- the estimated growth of the insulin market was uncertain and varied depending on the method used (underestimate or overestimate);
- the estimate of the market share for IDegAsp was associated with a high degree of uncertainty and was assumed with no evidence base (underestimate or overestimate); and
- the estimate of script equivalence ratios was uncertain due to uncertainty of the equi-effective doses and the lack of comparative data with some of the drugs being replaced (underestimate).

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

7 PBAC Outcome

7.1 The PBAC did not recommend insulin degludec with insulin aspart (IDegAsp) for treatment of adult patients with diabetes mellitus where insulin treatment is necessary on the basis that the cost effectiveness of the drug in type 2 diabetes mellitus (T2DM) was not established at the proposed price, and because the clinical place in type 1 diabetes mellitus (T1DM) was not established in the submission.

7.2 The PBAC acknowledged the clinical need for insulin products that improve glycaemic control whilst minimising the risk of hypoglycaemia. However, the Committee was not convinced that the evidence provided for IDegAsp demonstrated it fulfilled this role.

7.3 The PBAC noted that IDegAsp was not TGA registered at the time of its consideration. The PBAC also noted that IDeg as a single agent is currently undergoing TGA evaluation.

7.4 The PBAC noted that if listed, IDegAsp would be the first long acting/short acting premixed insulin available on the PBS. The PBAC considered there was a clinical place for IDegAsp in the treatment of T2DM but it was not certain if there was a clinical place for T1DM, as most T1DM patients are treated with basal/bolus regimens or insulin pumps. Thus, biphasic mixed insulins have an extremely limited role in this setting.

7.5 The PBAC considered that biphasic insulin aspart 30 (BIAsp 30) was an appropriate comparator in T2DM. However, the PBAC noted that the price requested for IDegAsp was higher than that for insulin glargine (IGlar) and that a clinical comparison against IGlar in T2DM may be informative in this context.

7.6 The PBAC considered that insulin detemir (IDet) was not the appropriate comparator in T1DM. The PBAC considered that BIAsp 30 or other pre-mixed insulins may be more appropriate comparators as they possess pharmacologic similarities.

7.7 The PBAC noted the risk of bias in the open label clinical trials presented in the submission and agreed that this risk was in part mitigated by the objective outcome measures of effectiveness such as HbA1c. However, the PBAC agreed that it was difficult to assess the likely impact of IDegAsp on overall rates of hypoglycaemia in clinical practice, particularly asymptomatic hypoglycaemia, as there would be less testing in the clinical environment than in a study environment. Additionally, the PBAC noted that blood glucose levels in the studies were measured using self-measuring devices rather than continuous blood glucose monitoring and therefore do not provide complete or accurate data of blood glucose levels over the whole dosing interval.

7.8 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonably supported by the data for T2DM.

7.9 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data (see paragraph 6.23)

7.10 The PBAC considered the inclusion of cost offsets for severe hypoglycaemic events in the price for IDegAsp to be inconsistent with the clinical evidence for safety (see paragraph 6.24).

7.11 The PBAC considered that the equi-effective doses in T2DM were uncertain (see paragraph 6.30).

7.12 The PBAC considered there was a high degree of uncertainty in the financial estimates (see paragraph 6.41). The PBAC noted that at the proposed price, the listing of IDegAsp would result in a higher cost to the PBS/RPBS due to the higher price of IDegAsp compared to the insulins replaced and because the cost offsets included in the price calculations are not included in the financial estimates.

7.13 The PBAC considered that any future major resubmission seeking a premium over BIAsp30 on the basis of an improved safety profile would need to clearly demonstrate the benefits over this drug, including providing more data on hypoglycaemic events.

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

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

Novo Nordisk remains committed to working with the PBAC to make Ryzodeg® 70/30 available for Australians with diabetes mellitus who would benefit from this product.