All Wales Therapeutics and Toxicology Centre
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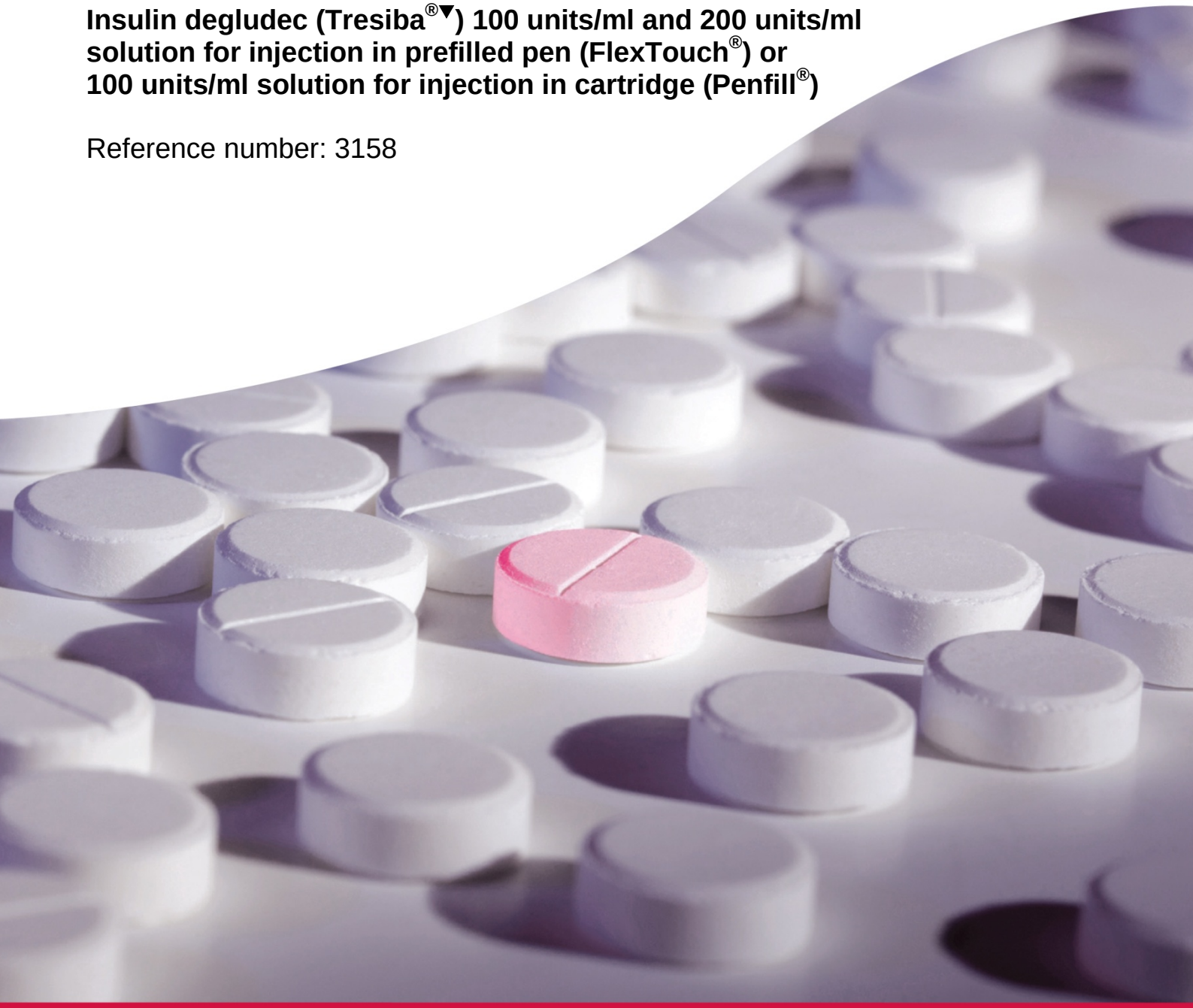
AWMSG SECRETARIAT ASSESSMENT REPORT

Insulin degludec (Tresiba®▼) 100 units/ml and 200 units/ml solution for injection in prefilled pen (FlexTouch®) or 100 units/ml solution for injection in cartridge (Penfill®)

Reference number: 3158



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AWMSG Secretariat Assessment Report
Insulin degludec (Tresiba®▼) 100 units/ml and 200 units/ml solution for injection in prefilled pen (FlexTouch®) or 100 units/ml solution for injection in cartridge (Penfill®)

This assessment report is based on evidence submitted by Novo Nordisk Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Insulin degludec (Tresiba®▼) for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year[2-4].
Dosing	Insulin degludec is administered once-daily by subcutaneous injection at any time of the day, with a minimum of eight hours between injections, but preferably at the same time of day. It is to be dosed in accordance with the individual patient's needs to optimise glycaemic control via dose adjustment based on fasting plasma glucose. In type 1 diabetes mellitus, it must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements. In type 2 diabetes mellitus, it can be administered alone, or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. Refer to the Summaries of Product Characteristics for further information regarding insulin degludec dosing[2-4].
Marketing authorisation date	30 January 2015 (licensed for the treatment of diabetes mellitus in adults on 21 January 2013)[2-4].

2.0 DECISION CONTEXT

2.1 Background

Diabetes mellitus is a chronic metabolic disorder characterised by high levels of blood glucose (hyperglycaemia)[5,6] which can, if prolonged, cause microvascular and macrovascular damage in the body[7]. The National Institute for Health and Care Excellence (NICE) has issued guidelines for the management of type 1 diabetes mellitus (T1DM)[5] and type 2 diabetes mellitus (T2DM)[6]. In adults with T1DM, NICE recommend offering multiple daily injection basal-bolus insulin regimens as the insulin injection regimen of choice and twice-daily insulin detemir as the basal insulin therapy. As an alternative to twice-daily detemir, the following can be considered: once daily insulin glargine or insulin detemir if twice-daily insulin injection is not acceptable, or once daily insulin glargine if insulin detemir is not tolerated[5]. In adults with T2DM, when starting insulin therapy, NICE recommend offering Neutral Protamine Hagedorn (NPH) insulin injected once or twice daily, and, to consider as an alternative, using insulin detemir or insulin glargine under certain circumstances (e.g. when hypoglycaemia is a problem), or pre-mixed (biphasic) preparations that include short-acting insulin analogues. NICE also recommend the option of switching to insulin detemir or insulin glargine from NPH insulin in certain circumstances in patients with T2DM[6].

Insulin degludec (Tresiba®▼) is a long-acting basal insulin analogue[8]. On subcutaneous injection it forms a depot of soluble multi-hexamers, which allow insulin to be slowly and continuously absorbed into the circulation[8]. The All Wales Medicines Strategy

Group (AWMSG) has previously appraised insulin degludec (Tresiba®▼) for the treatment of diabetes mellitus in adults and issued a non-recommendation for this indication[9]. An updated AWMSG submission has been made for insulin degludec which includes a new list price and additional information[1]. Since the original submission, the licensed indication has been extended to include adolescents and children from the age of 1 year[2-4]; however, the applicant company has highlighted that the resubmission focuses on the use of insulin degludec for adult patients with diabetes mellitus where treatment with a basal insulin analogue is considered appropriate[1].

2.2 Comparators

The comparator included in the company submission was insulin glargine (Lantus®)[1].

2.3 Guidance and related advice

- NICE pathway. Managing blood glucose in adults with type 2 diabetes (2016)[10].
- NICE guideline 28 (NG28). Type 2 diabetes in adults: management (2015)[6].
- NICE guideline 17 (NG17). Type 1 diabetes in adults: diagnosis and management (2015)[5].
- Welsh Government. Together for health – a diabetes delivery plan. A delivery plan up to 2016 for NHS Wales and its partners (2013)[11].
- Inzucchi SE, Bergenstal RM, Buse J et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (2012)[12].
- All Wales Consensus Group on Diabetes Care Guidelines. Designed for the management of adults with diabetes mellitus across Wales: consensus guidelines (2008)[13].

AWMSG has previously issued a non-recommendation for the use of insulin degludec (Tresiba®▼) for the treatment of diabetes mellitus in adults, stating that the applicant company did not present sufficiently robust clinical and economic analyses to gain approval[9].

AWMSG has previously issued recommendations for the use of insulin degludec/liraglutide (Xultophy®▼)[14] and insulin glargine (Abasaglar®▼)[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In their submission, the company discussed the clinical effectiveness of eight phase III therapeutic confirmatory studies (T1DM: 3583, 3585 and 3770; T2DM: 3579, 3672, 3586, 3668, and 3582) to enable a comparison between insulin degludec and insulin glargine or insulin detemir[1]. The company also included five extension studies, meta-analyses, and two further studies, in support of clinical efficacy. Clinical safety focused on pooled data from 11 therapeutic confirmatory studies[1].

3.1 Confirmatory studies

3.1.1 T1DM

Studies 3583[16], 3585[17] and 3770[18] were randomised, controlled, parallel-group, open-label, multicentre, multinational, treat-to-target studies (see Glossary) which compared once daily insulin degludec with once daily insulin glargine (study 3583) or insulin detemir (study 3585) in adult patients (≥ 18 years of age) diagnosed clinically with T1DM for ≥ 12 months (baseline HbA_{1c} set at ≤ 10.0%) with a study duration of 26 weeks (3585 and 3770) or 52 weeks (3583)[16-19]. In study 3770, insulin degludec, dosed in the morning or in the evening on alternating days (fixed flexible dosing), was compared to once daily insulin glargine or insulin degludec (non-fixed flexible dosing)[18]. Patients who were treated with basal-bolus insulin for ≥ 12 months were included; however, patients with a history of recurrent severe hypoglycaemia (more than one

severe hypoglycaemic episode during the last 12 months), or unawareness of hypoglycaemia or hospitalisation for diabetic ketoacidosis during the previous six months, or cardiovascular disease within the last six months, were excluded[1,19]. Only concomitant treatment with mealtime insulin aspart was allowed[19].

The primary endpoint was to confirm the efficacy of insulin degludec in controlling glycaemia, as measured by mean change from baseline HbA_{1c} compared with insulin glargine (studies 3583 and 3770) or insulin detemir (study 3585)[16-19]. Noninferiority of insulin degludec (including fixed flexible dosing in study 3770) compared to insulin glargine and insulin detemir was demonstrated (upper limit of the 95% confidence interval [CI] ≤ 0.4%), thus the primary endpoint was met in all studies (see Table 1 for results)[19]. The change in observed HbA_{1c} from baseline to end of study ranged from approximately 0.4% to 0.7% points for both insulin degludec and comparator, thus clinically relevant reductions in HbA_{1c} were observed taking the relatively low baseline HbA_{1c} into account. Mean HbA_{1c} of 7.2% to 7.4% at end of trial was obtained with both insulin degludec and comparator products in all studies[19].

Secondary endpoints included the proportion of subjects reaching pre-specified HbA_{1c} targets with or without hypoglycaemia, laboratory-measured fasting plasma glucose (FPG), 9-point self-measured plasma glucose (SMPG) profiles and health-related quality of life (HRQoL)[19]. These were supportive of the primary endpoint[19].

Table 1. Results from studies 3583, 3585 and 3770[19].

	Insulin degludec		Comparator		Treatment difference (95% CI)	Conclusion
Endpoints	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**		
Study 3583*						
HbA_{1c} (%) change from baseline at end of study (52 weeks)	472	−0.36 (0.05)	157	−0.34 (0.07)	−0.01 (−0.14 to 0.11)	Noninferior
Study 3585†						
HbA_{1c} (%) change from baseline at end of study (26 weeks)	302	−0.71 (0.06)	153	−0.61 (0.07)	−0.09 (−0.23 to 0.05)	Noninferior
Study 3770* (including fixed flexible dosing)						
HbA_{1c} (%) change from baseline at end of study (26 weeks)	164§	−0.40 (0.05)	164¶	−0.57 (0.05)	0.17 (0.04 to 0.30)	Noninferior
			165**	−0.41 (0.05)	0.01 (−0.13 to 0.14)	Noninferior

CI: confidence interval; LS mean: least-squares mean; N: number of patients contributing to analysis; SE: standard error.

*Basal-bolus therapy, insulin degludec versus insulin glargine.
†Basal-bolus therapy, insulin degludec versus insulin detemir.
§Insulin degludec fixed flexible dosing.
¶Insulin glargine.
**Insulin degludec non-fixed flexible dosing.

3.1.2 T2DM

Studies 3579[20], 3586[21], 3672[22], 3668[23] and 3582[24] were randomised, controlled, parallel-group, open-label, multicentre, multinational, treat-to-target studies which compared once daily insulin degludec with once daily insulin glargine in adult patients (≥ 18 years of age) diagnosed clinically with T2DM for ≥ six months. Patients either

received basal oral therapy (studies 3579, 3586, 3672, 3668) or basal-bolus ± oral antidiabetic (OAD) therapy (study 3582). Baseline HbA_{1c} was set at 7.0%–10.0% for all studies, with the exception of study 3668 where the baseline was 7.0%–11.0% for insulin-naïve patients and 7.0%–10.0% for insulin-treated patients. Study duration was 26 weeks (3672, 3586, 3668) or 52 weeks (3579, 3582)[19-24]. Study 3668 included a third treatment arm in which insulin degludec was dosed in the morning or in the evening on alternating days (fixed flexible dosing)[23]. Patients who were treated with monotherapy or combination OAD therapy for ≥ three months were included with the exception of study 3668 (treated with OADs and/or basal insulin) and study 3582 (treated with any insulin treatment ± OADs). However, patients with a history of recurrent severe hypoglycaemia (more than one severe hypoglycaemic episode during the last 12 months), or unawareness of hypoglycaemia or hospitalisation for diabetic ketoacidosis during the previous six months, or cardiovascular disease within the last six months, were excluded[1,19].

The primary endpoint was to confirm the efficacy of insulin degludec in controlling glycaemia, as measured by change from baseline HbA_{1c} compared with insulin glargine[19-24]. Treatment with insulin degludec resulted in clinically relevant reductions in mean HbA_{1c}, ranging from approximately 1.1% to 1.4% points compared to 1.1% to 1.5% points with insulin glargine[19]. The mean observed HbA_{1c} at end of study was between 7.0% and 7.3% with insulin degludec and between 6.9% and 7.2% with insulin glargine[19-24]. Noninferiority to insulin glargine was confirmed in all studies as the upper limits of the 95% CI for the estimated treatment difference was ≤ 0.4% for all the estimated treatment differences of change in HbA_{1c}, thus the primary endpoint was met in all studies (see Table 2 for results)[19].

Secondary endpoints included the proportion of subjects reaching pre-specified HbA_{1c} with or without hypoglycaemia, laboratory-measured FPG, 9-point SMPG profiles and HRQoL[19]. These were found to be supportive of the primary endpoint[19].

Table 2. Results from studies 3579, 3586, 3672, 3668 and 3582[19].

Endpoints	Insulin degludec		Comparator		Treatment difference (95% CI)	Conclusion
	N	LS Mean (SE)	N	LS Mean (SE)		
Study 3579: Basal oral therapy						
HbA_{1c} (%) change from baseline at end of study (52 weeks)	773	−1.06 (0.04)	257	−1.15 (0.06)	0.09 (−0.04 to 0.22)	Noninferior
Study 3586: Basal oral therapy						
HbA_{1c} (%) change from baseline at end of study (26 weeks)	289	−1.42 (0.06)	146	−1.52 (0.07)	0.11 (−0.03 to 0.24)	Noninferior
Study 3672: Basal oral therapy						
HbA_{1c} (%) change from baseline at end of study (26 weeks)	228	−1.18 (0.09)	229	−1.22 (0.08)	0.04 (−0.11 to 0.19)	Noninferior
Study 3668: Basal oral therapy (including fixed flexible dosing)						
HbA_{1c} (%) change from baseline at end of study (26 weeks)	229†	−1.17 (0.08)	230*	−1.21 (0.08)	0.04 (−0.12 to 0.20)	Noninferior
			228§	−1.03 (0.08)	−0.13 (−0.29 to 0.03)	Noninferior
Study 3582: Basal-bolus therapy ± OADs						
HbA_{1c} (%) change from baseline at end of study (52 weeks)	744	−1.10 (0.06)	248	−1.18 (0.08)	0.08 (−0.05 to 0.21)	Noninferior

†Insulin degludec fixed flexible dosing.
*Insulin glargine.
§Insulin degludec non-fixed flexible dosing.

3.1.3 Extension studies

The company submission also included details of five extension studies (T1DM: 3644[25], 3770[18] and 3725[26]; T2DM: 3643[27] and 3667[28]). Studies were randomised, controlled, open-label, multicentre, multinational, two arm, parallel, treat-to-target studies, which were designed to assess the long-term efficacy and safety of insulin degludec[1,18,25-27]. The extension studies were found to be supportive of the confirmatory studies with similar efficacy results observed for up to 104 weeks[1,18,25-28].

3.1.4 Meta-analyses

As the individual confirmatory studies were not powered to show differences in the secondary endpoints, a prospectively planned meta-analysis of hypoglycaemic episodes, pooling the therapeutic confirmatory trials with insulin glargine (once daily dosing) as the comparator was performed[1]. Data from study 3585 were excluded as the comparator was not insulin glargine. The data from the insulin degludec fixed flexible arms in studies 3770 and 3668 were also excluded. Meta-analyses were also performed for HbA_{1c}, FPG, insulin dose and HRQoL. These analyses used a negative binomial regression model adjusted for study, diabetes type, antidiabetic therapy at screening, sex, geographical region and age[1].

In the pre-specified meta-analysis of hypoglycaemia, the primary endpoint was the total number of treatment-emergent confirmed hypoglycaemic episodes; the analysis demonstrated that insulin degludec was superior to insulin glargine with an estimated rate ratio of 0.91 (95% CI: 0.83 to 0.99)[19,29]. The rates were primarily driven by statistically significant results in T2DM (estimated rate ratio 0.83 [95% CI: 0.74 to

0.94])[19,29], whereas there was no statistically significant difference in T1DM (estimated rate ratio 1.10 [95% CI: 0.96 to 1.26])[1,19,29]. Similar results were observed for the analysis of nocturnal hypoglycaemia, i.e. significantly favouring insulin degludec (estimated rate ratio 0.74 [95% CI: 0.65 to 0.85]), but driven by statistically significant results in T2DM (estimated rate ratio 0.68 [95% CI: 0.57 to 0.82])[29]; the estimated rate ratio in T1DM was 0.83 (95% CI: 0.69 to 1.00)[1,29]. For severe hypoglycaemic episodes, the estimated rate ratio was only statistically significantly lower for insulin degludec in insulin-naive T2DM patients[29].

The results of the additional meta-analyses were overall consistent with the results of the confirmatory studies[19].

3.1.5 Supporting evidence

The company submission included evidence from one observational and one retrospective study. In Sweden, a prospective, open-label, single-arm, observational, clinical follow-up of patients with T1DM (n = 357), showed that mean HbA_{1c} decreased from 68.9 mmol/mol (standard deviation [SD]: 15.7) to 65.8 mmol/mol (SD: 14.3) ($p < 0.0001$) in patients switching from insulin glargine (n = 216), insulin detemir (n = 131), NPH insulin (n = 5) or continuous subcutaneous insulin infusion (n = 5) to insulin degludec (median time to follow-up was 20 weeks)[30]. This improvement was despite a 14% reduction in the total basal insulin dose (data from 352 patients). The numbers of overall and nocturnal self-reported hypoglycaemic events (from 349 patients with complete data) were also reduced (from 8.2 [SD: 8.9] to 6.4 [SD: 7.6] events/patient/four weeks [$p < 0.0001$], and from 1.6 [SD: 2.9] to 0.7 [SD: 2.0] events [$p < 0.0001$], respectively)[30]. In the UK, a retrospective, single-centre, case series analysis of patients with T1DM (n = 35) or T2DM (n = 16) showed that mean HbA_{1c} significantly decreased in patients switching from insulin glargine or insulin detemir to insulin degludec (T1DM: decreased by 0.52 [SD: 0.32] % points; T2DM: by 0.68 [SD: .25] % points)[31]. The rate of hypoglycaemic events per week decreased by 90.7% for patients with T1DM and 90.3% for patients with T2DM[31].

3.2 Safety

The evaluation of clinical safety was primarily focused on pooled safety data from 11 insulin degludec studies. In total, 4,275 patients were exposed to insulin degludec: 3,758 patients for at least six months and 1,635 patients for at least 12 months[19]. The Committee for Medicinal Products for Human Use (CHMP) noted that insulin degludec had a safety profile similar to that of other marketed insulin products. The proportion of patients with T1DM and T2DM reporting treatment-emergent adverse events (TEAEs) and the rate of TEAEs were similar for insulin degludec (T1DM: 77.3%; T2DM: 68.3%) and comparators (T1DM: 76.2%; T2DM: 65.1%). Adverse events (AE) were of mild or moderate severity and the pattern was generally similar between groups. The most frequently reported occurring AE in both treatment groups were nasopharyngitis, upper respiratory infections, headache and diarrhoea[19].

Hypoglycaemic events were only recorded as AEs if they fulfilled the definition of either serious adverse events (SAEs) or severe hypoglycaemia[1,19]. Hypoglycaemic events, defined as SAEs, were slightly more common in the insulin degludec group versus the comparator; however, the rates of severe hypoglycaemia were similar[19]. The proportion of patients with T1DM and T2DM who reported SAEs and the rate of SAEs were similar for insulin degludec (T1DM: 8.0%; T2DM: 7.8%) and comparators (T1DM: 7.1%; T2DM: 6.3%). The proportion of patients discontinuing due to AEs were low for both insulin degludec (2.3%) and comparators (1.3%). Hypoglycaemia was the most common reason for withdrawal in subjects with T1DM whereas cardiovascular disorders and increases in weight were reported more frequently in patients with T2DM[19].

3.3 AWTTC critique

- Insulin degludec is indicated for the treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year. No paediatric data has been submitted by the applicant company. The company has suggested that insulin degludec be considered as a treatment option for adults with diabetes mellitus where treatment with a basal insulin analogue is considered appropriate[1]. NICE Clinical Guidelines recommend the use of a basal-bolus regimen as the insulin injection regimen of choice in adults with T1DM, and a range of basal insulin regimen options in patients with T2DM for when insulin therapy is required[5,6].
- The company consider insulin glargine (Lantus®) as the most appropriate comparator stating it is the most widely used basal analogue in Wales[1]. However, in line with NICE recommendations and clinical expert opinion, insulin detemir, Abasaglar® (a biosimilar insulin glargine) and Toujeo® (a high-strength insulin glargine) may also be appropriate comparators. Insulin detemir is reported to account for over 20% of the market share of basal insulins; this figure is supported by Welsh prescribing data obtained by AWTTC. The company did not provide comparative efficacy or safety data for insulin degludec versus Abasaglar® or Toujeo® in patients with T1DM or T2DM, or versus insulin detemir in patients with T2DM.
- In both T1DM and T2DM patients, the rate of confirmed and nocturnal hypoglycaemia was lower with insulin degludec than with the comparator. However, these were not statistically significant across both T1DM and T2DM; therefore, CHMP concluded that no claims on an overall reduction of the risk of hypoglycaemia can be made[19]. Furthermore, nocturnal hypoglycaemic events were statistically significantly reduced with insulin degludec compared with insulin glargine with a pre-defined six hour window; however, insulin degludec dosing was only permitted in the evening in the studies, in contrast to insulin glargine that could be dosed anytime. The US Food and Drug Administration (FDA) requested additional analyses that widened the period for counting nocturnal events to eight hours in T1DM patients: no advantage for insulin degludec over insulin glargine was apparent[32]. CHMP highlighted that no direct comparison of hypoglycaemia rates by dosing time can be made between insulin degludec and insulin glargine[19].
- The confirmatory studies of insulin degludec specifically excluded patients with a history of recurrent severe hypoglycaemia, or unawareness of hypoglycaemia, or cardiovascular disease within the last six months, defined as: stroke; decompensated heart failure (New York Heart Association [NYHA] class III or IV); myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty[1]. The applicability of the trial results to all patients eligible for treatment is therefore unknown. However, data from one observational study and one retrospective study submitted by the company provide support for the use of insulin degludec in clinical practice[30,31].
- At the time of licensing insulin degludec (Tresiba®▼), CHMP highlighted that a limitation of existing insulin therapy is that injection devices only allow administration of a maximum 80 units per injection and administration of large volumes (> 1 ml) have been associated with pain or discomfort[19]. Insulin degludec is available in two strengths, 100 units/ml and 200 units/ml, allowing patients to take up to 160 units of insulin degludec in a single injection. The applicant company has a series of recommendations for healthcare professionals to reduce the risk of medication errors with insulin degludec. There are now several other high strength insulin products on the market[33]. In 2015, the risks associated with high strength insulin products and strategies to reduce these risks were highlighted by the Medicines and Healthcare products Regulatory Agency[33]. The European Medicines Agency has also issued guidance on prevention of medication errors with high-strength insulins[34].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost-utility analysis (CUA) of insulin degludec (Tresiba®) versus insulin glargine (Lantus®) in three separate groups of adult patients:

- T1DM using a basal-bolus insulin regimen ($T1DM_{B/B}$)
- T2DM who are on a basal oral therapy regimen with a long acting insulin analogue ($T2DM_{BOT}$)
- T2DM using a basal-bolus insulin regimen ($T2DM_{B/B}$)

The company submission includes a new list price for insulin degludec and focuses on a subgroup of the full licensed indication i.e. all adult type 1 and type 2 diabetes populations where treatment with a basal insulin analogue is considered appropriate. Insulin glargine (Lantus®) is the only comparator considered in the base case analyses, on the basis that it accounts for 67% of the current basal insulin market in Wales[1]. Alternative comparators explored via scenario analyses include insulin glargine 300 (Toujeo®) and insulin glargine biosimilar (Abasaglar®) but not insulin detemir (Levemir®), which is known to be used in Wales[1].

The base case CUAs consider the impact of hypoglycaemic events on health-related quality of life, and the costs of insulins, needles, test strips and resource use associated with hypoglycaemic events. It was assumed that other costs of treatment, other costs resulting from treatment and self-measured blood glucose (SMBG) testing (unrelated to hypoglycaemia) were equivalent in both treatment groups. The analysis adopts an NHS/Personal Social Services perspective and a one-year time horizon. The justification for the time horizon is that insulin degludec trials were designed to treat patients to glycaemic target. Consequently, there are no differences in glycaemic control to model differential long-term outcomes. It is therefore argued that longer time frames would merely repeat the one-year findings[1].

All analyses employ the new Department of Health agreed list price for insulin degludec. The cost of insulin degludec is calculated as £416 per patient per annum, which is lower than the annual cost per patient for insulin glargine (£423). These insulin costs are based on the doses observed in clinical trials (using dose ratios derived from a meta-analysis[35], adjusted for differences in confounding factors such as gender and body weight). The doses for use in T1DM have been further validated against Swedish observational data[30,36].

Baseline risks of hypoglycaemic events in patients with T1DM and T2DM administered insulin glargine were taken from the UK Hypoglycaemia Study Group observational study[37]. The relative risks of non-severe daytime, non-severe nocturnal (between 12 am and 6 am), and severe (any time) hypoglycaemic events for those administered insulin degludec were derived from meta-analyses[29,35] (see section 3.1.4 for details). Only statistically significant differences are included in the model to avoid random variation influencing the results.

The costs associated with hypoglycaemic events are sourced from published literature[38,39]. Underlying resource use was analysed in two European studies, which included patients from the UK. One study gathered data on severe hypoglycaemic events from 319 patients with T1DM and 320 with T2DM[38]. The second study analysed resource use for 18,893 non-severe hypoglycaemic events[39]. The company assumed no difference between the management of hypoglycaemic events for insulin glargine or insulin degludec. Therefore, any differences in the hypoglycaemia-related costs between insulin degludec and insulin glargine are attributable only to the modelled differential rates of these events. Quality-adjusted life years (QALYs) were calculated

by applying a disutility to each hypoglycaemic event, taken from a single study, involving an international sample of the general population[40].

A range of sensitivity and scenario analyses have been conducted, including: rates of hypoglycaemic events based on other sources, clinical trial data and recent observational data[41], alternative distributions of nocturnal hypoglycaemic events, utility values for flexible dosing, costs of therapy and needles, dosing and injection frequency, alternative sources for costing hypoglycaemic events, and alternative comparators.

4.1.2 Results

The results of the base case analyses are detailed in Table 3. The analyses reveal that in patients with T1DM, when compared with insulin glargine, insulin degludec dominates (i.e. insulin degludec is more effective and less costly); the main cost driver in this instance being insulin costs. The cost and QALY differences associated with hypoglycaemic events slightly favour insulin degludec.

Insulin acquisition costs are higher for insulin degludec than for insulin glargine for $T2DM_{BOT}$. However, these extra costs are more than offset by lower hypoglycaemic event costs; in particular, lower severe hypoglycaemic events. Reductions in severe hypoglycaemic events are reflected in the QALY differences reported.

Insulin acquisition costs are approximately £140 higher for insulin degludec than for insulin glargine for $T2DM_{B/B}$ and remain largely uncompensated by the relative advantages of insulin degludec on non-severe daytime glycaemic events. Notably, the ICER for insulin degludec versus insulin glargine for $T2DM_{B/B}$ amounts to £16,352 per QALY gained, whereas insulin degludec dominates (lower costs, QALY gains) for both other groups.

Table 3: Results of the base case analyses.

	Insulin degludec (Tresiba®)	Insulin glargine (Lantus®)	Difference
T1DM Basal-bolus therapy			
Total costs	1,263.89	1,304.16	−40.27
Total QALYs	0.6302	0.6258	0.0044
ICER (£/QALY gained)	Insulin degludec dominant		
T2DM Basal oral therapy			
Total costs	577.81	604.67	−26.86
Total QALYs	0.8843	0.8770	0.0073
ICER (£/QALY gained)	Insulin degludec dominant		
T2DM Basal-bolus therapy			
Total costs	1,772.10	1,633.95	138.16
Total QALYs	0.8014	0.7930	0.0084
ICER (£/QALY gained)	£16,352/QALY		

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

The company provides various sensitivity and scenario analyses. Univariate sensitivity analyses indicate that results for $T1DM_{B/B}$ are sensitive to changes in dosing ratios and prices (e.g. when the price for insulin glargine is reduced by 15%, insulin degludec no longer dominates – the resultant ICER is £2,245 per QALY gained). For $T2DM_{BOT}$ similar sensitivities exist, most prominently for price changes; a 15% price decrease in

insulin glargine produces an ICER of approximately £7,000 per QALY gained. For $T2DM_{B/B}$, the ICER increases close to £30,000 per QALY gained in response to the same price change. In two-way sensitivity analyses ICERs surpass £30,000 per QALY gained. For example, the combinations of lower insulin glargine pricing plus lower disutilities (see Table 4). Finally, the scenarios including insulin glargine biosimilar Abasaglar® as the comparator produced similar ICERs for all three indications as the 15% price reduction for insulin glargine (Lantus®). Except for the selected analyses specified in Table 4, results were relatively robust in indicating cost savings or at least cost-effectiveness below £20-30,000 per QALY gained, although there are some concerns with the probabilistic sensitivity analysis (PSA) (see below).

Table 4: Selected (worse case) results of the deterministic sensitivity and scenario analyses.

Scenario	ICER (£/QALY gained)	Plausibility
T1DM Basal-bolus therapy		
Equal dosing	£9,031	Unlikely alternative scenario, given that lower dosing is reflective of the current evidence base
Versus Abasaglar® or price insulin glargine (Lantus®) -15%	£2,245	Highly plausible alternative scenario given that biosimilar insulin glargine is available in Wales
T2DM Basal oral therapy		
Price insulin glargine (Lantus®) -15% and other source disutilities	£22,565	Possible alternative, as various sources for utilities exist other than those used in the base case
Versus Abasaglar® or price insulin glargine (Lantus®) -15%	£7,069	Highly plausible alternative scenario given that biosimilar insulin glargine is available in Wales
T2DM Basal-bolus therapy		
Price insulin glargine (Lantus®) -15% & other source disutilities	£37,057	Possible alternative, as various sources for utilities exist other than those used in the base case
Versus Abasaglar® or price insulin glargine -15%	£28,300	Highly plausible alternative scenario given that biosimilar insulin glargine is available in Wales
ICER: incremental cost effectiveness ratio; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; QALY: quality-adjusted life-year;		

The results of the PSA are detailed in Table 5. For $T1DM_{B/B}$, approximately 40% of the simulations indicate QALY losses for insulin degludec whereas 100% indicate cost savings. For $T2DM_{BOT}$, QALY gains are almost 100% positive and approximately 93% of simulations indicate cost savings. Finally, for $T2DM_{B/B}$, 10% of simulations indicate QALY losses and none indicate cost savings. Uncertainty may have been underestimated due to the fact that only significantly differing variables from the trials were included in the PSA.

Table 5: Results of the probabilistic sensitivity analyses.

Treatment group	Probability of the treatment pathway containing insulin degludec being cost-effective at a WTP threshold of	
	£20,000	**£30,000**
T1DM Basal-bolus therapy	**63.0%**	**61.7%**
T2DM Basal oral therapy	**99.8%**	**99.8%**
T2DM Basal-bolus therapy	**59.3%**	**73.4%**
T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; WTP: willingness to pay.		

4.1.3 AWTTC critique

The company has targeted its analyses to differentiate between three patient groups. QALY gains and cost savings for insulin degludec over insulin glargine differ between these groups. The modelled advantage of insulin degludec relates to assumed reductions in hypoglycaemic events (notably in T2DM) and lower dosing (notably in T1DM). However, the reduced risk of nocturnal hypoglycaemic events with insulin degludec over insulin glargine may be driven by the trial protocols. In a plausible scenario of no advantage of insulin degludec over insulin glargine in T2DM, insulin degludec would be more costly. The PSA reveals that while the cost-savings of insulin degludec are well supported for T1DM, 40% of the simulations indicate QALY losses.

Strengths of the economic evidence include:

- The company has adopted a pragmatic approach in modelling the cost effectiveness of insulin degludec over the short-term, which makes the model attractively non-complex and transparent.
- A range of sensitivity and scenario analyses have been conducted, using a range of alternative data sources, to explore some of the key parameter assumptions in the model.

Limitations of the economic evidence include:

- The model is restricted to a comparison with insulin glargine (Lantus®) which is questionable given that insulin detemir is reported to account for over 20% of the market share in Wales[1]. Furthermore, the introduction of less costly biosimilar insulins in Wales is not captured by the base case model (limited to scenario analysis) despite NICE recommendations[6] suggesting that they may also be appropriate comparators.
- Observational data on sizeable patient populations supporting the findings from the trials are only available for T1DM[30]. Notably, this applies to dosing and hypoglycaemic events.
- Not all uncertainties are included in the PSA, in particular those for some types of hypoglycaemic events are lacking. A more comprehensive approach to testing the sensitivities of these parameters would have reduced associated uncertainty.
- The costs associated with hypoglycaemic events are sourced from the UK components of two European studies, and are therefore likely to be representative of the Welsh population. However, the costs associated with severe episodes have not been inflated. This introduces an element of costing bias.
- For the T1DM analysis:
  - Some data in the model are taken from a patient population who have experienced one or more severe hypoglycaemic events[38]. However, other key trials providing parameter estimates in the model excluded patients experiencing more than one severe hypoglycaemic event in the last 12 months or those with impaired awareness of hypoglycaemia. It is unclear how representative these patients are of the target populations.
  - Only statistically significant relative risks of hypoglycaemia were included in the model, which precludes assessment of uncertainty in key parameters. Numerically higher risks of non-severe daytime and severe hypoglycaemic events observed with insulin degludec compared with insulin glargine are not considered.
  - Nocturnal hypoglycaemic events were statistically significantly reduced with insulin degludec compared with insulin glargine when defined as those events occurring in a six hour window between 12 am and 6 am. However, insulin degludec dosing was only permitted in the evening in the trials, in contrast to insulin glargine that could be dosed anytime. Prior analyses by the FDA suggest that an eight hour window results in no advantage for insulin degludec over insulin glargine[32]. It would therefore have been beneficial to have conducted sensitivity analysis on this time frame to analyse how far potentially observed differences could be driven by the trial protocol and definitions.

- For the T2DM analyses:
  - There was a lack of observational data on the relevance of lower dosing for $T2DM_{BOT}$.
  - The key trials providing parameter estimates in the model were conducted in insulin-naive patients. The extent to which the results from these trials would reflect results in the target populations is unclear.
  - Rates of severe hypoglycaemic events in the meta-analysis[35] are based on only one trial (3579) because severe event rates were too few in other trials, reflecting the low risk of hypoglycaemia in the trial populations. Yet, this rate fully determines the cost savings for the $T2DM_{BOT}$ indication; ergo, it is crucial for this indication.
  - The included trials specified the evening dosing of insulin degludec but permitted insulin glargine dosing at any time. The extent to which these data would reflect the relative risks of hypoglycaemia when insulin degludec is used more flexibly is unclear. No observational data exists for T2DM on this matter.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified two published CUAs conducted from a UK NHS perspective (using data sources also used in this submission), comparing insulin degludec with insulin glargine in patients with T1DM on basal/bolus ($T1DM_{B/B}$) and T2DM receiving only basal insulin ($T2DM_{BOT}$)[36,42]. The study on $T2DM_{BOT}$ used data from the meta-analysis of three phase III trials (inclusive of reduced dosing) and a 12-month time horizon of analysis. Utility estimates were based on disutiity values derived from the literature, and an alternative approach using SF-36 data from the clinical trials. An additional utility gain was applied in both models for the assumed increase in dosing flexibility with insulin degludec (explaining up to approximately half of the QALY gain). In the base case model ICERs were approximately £13,000 and £15,800 per QALY gained, depending on the source of utility values. A scenario analysis restricting use to a subgroup of patients who experienced ≥ 1 hypoglycaemic event(s) per year reduced the ICERs to around £2,600 and £4,900 per QALY gained. Given that the cost of insulin degludec was higher than the new list price used in this CUA, the differences between costs reported when compared with this submission are easily explained.

A full paper reflecting a CUA of insulin degludec compared with insulin glargine in people with T1DM, conducted from the UK NHS perspective, has also been identified[36]. This analysis used a 12-month time horizon of analysis and disutilities for hypoglycaemias derived from several sources, including the study used for the disutilities in this submission[40]. The authors also incorporated the utility gain associated with greater dose flexibility in to the model in their sensitivity analysis. The base case ICER was estimated to be £16,895 per QALY gained, ranging from £6,532 to £32,341 depending on the utility approach adopted. Base case QALY gain per patient was estimated to be double than the current submission (0.0044 versus 0.0082). The cost of insulin degludec in these analyses again does not reflect the currently agreed list price, whereas lower dosing seems to have been included as in the present analysis. When equal dosing was assumed, insulin degludec was borderline cost-effective (£20,714–£29,920/QALY).

SMC has previously assessed insulin degludec[43]. T2DM groupings were different from this current Welsh submission, not allowing sensible comparisons with T2DM patient groups. The core findings for the T1DM group were based on higher pricing for insulin degludec than in this present submission: QALY gains presented are identical. A relevant critique concerned the use of disutilities for hypoglycaemias that were higher than those used in previous SMC submissions on T1DM patient populations. Overall, the conclusion for insulin degludec was that *"the economic case has not been demonstrated*".

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on UK figures the company assumes that 7.54% of the population of Wales has diabetes, of which 10% has T1DM and 90% has T2DM[44-46]. An incidence rate of 0.01% for T1DM and 0.38% for T2DM is assumed based on Scottish survey data[47], and mortality rates of 1.63% for T1DM and 3.62% for T2DM are assumed based on English audit data[48,49]. This equates to 18,323 people with T1DM and 170,439 people with T2DM in year one, increasing to 19,471 and 216,034, respectively in year five. For $T1DM_{B/B}$, $T2DM_{BOT}$ and $T2DM_{B/B}$ eligible patient populations are estimated to increase at a constant rate from year one to five from 11,620 to 12,348, from 4,210 to 5,337 and from 6,685 to 8,474, respectively.[19] Using an assumed increased uptake of insulin degludec (differing for the three indications) and 5% discontinuation rate, this would translate into an increase between year one to five from: 1,104 to 4,692 for $T1DM_{B/B}$; 200 to 1,267 for $T2DM_{BOT}$; and 191 to 1,207 for $T2DM_{B/B}$.

Acquisition costs are based on MIMS for the comparators and the new list price for insulin degludec. For insulin degludec, unit costs are combined with the average daily doses reported at the end of clinical trials and corresponding with the lower dosing that was assumed in the cost-effectiveness analysis for $T1DM_{B/B}$ and $T2DM_{BOT}$ (higher for $T2DM_{B/B}$). The comparators used in the budget impact model include not only insulin glargine as in the CUA base case, but also insulin detemir and insulin aspart. When these medicines are displaced as a result of the introduction of insulin degludec this produces cost savings in the analysis, as detailed below.

5.1.2 Results

Table 6 presents the net uptake and cost estimates provided by the company. Cost savings of £16,452 and £12,315 are predicted for years one and five respectively.

Table 6: Company budget impact estimates.

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Potential number of eligible patients (indications covered in this submission)					
T1DM Basal-bolus therapy	11,620	11,802	11,984	12,166	12,348
T2DM Basal oral therapy	6,685	7,132	7,579	8,026	8,474
T2DM Basal-bolus therapy	6,685	7,132	7,579	8,026	8,474
Uptake (%)					
T1DM Basal-bolus therapy	10.00%	20.00%	30.00%	35.00%	40.00%
T2DM Basal oral therapy	5.00%	10.00%	15.00%	20.00%	25.00%
T2DM Basal-bolus therapy	3.00%	6.00%	9.00%	12.00%	15.00%
Treated patients	1,494	3,076	4,744	5,921	7,167
Per patient cost in current market	£666	£668	£671	£680	£688
Per patient cost in new market with insulin degludec	£655	£658	£662	£675	£686
Net cost	−£16,452	−£30,592	−£42,419	−£28,868	−£12,315
Cumulative net cost	**−£16,452**	**−£47,044**	**−£89,463**	**−£118,331**	**−£130,646**

Sensitivity analyses indicate that the cost of insulin degludec, insulin degludec dose, cost of insulin glargine, and the displacement of insulin aspart are the most influential parameters in the analyses.

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of eligible patients in Wales. However, in the absence of Welsh data, these rely on Scottish survey and English Audit data.
- A number of assumptions are made in terms of uptake and discontinuation figures, which are subject to uncertainty.
- The budget impact model incorporates a wider range of comparators than the CUA. There is no clear justification or rationale provided for this change in approach. Notably, justification of savings on insulin aspart is lacking and associated assumptions are not in line with the cost-effectiveness analysis; despite the displacement of insulin aspart being highly influential in the budget impact according to the sensitivity analysis.
- The costs included in the model are limited to medicine acquisition costs. No consumables (needles, test strips) have been considered. It would have been beneficial to include these to achieve further optimal aligning with the cost-effectiveness analysis.
- Inclusion of insulin detemir in the cost offsets due to displaced medicines is not in line with the cost-effectiveness model that excludes any analysis including insulin detemir.

5.2 Comparative unit costs

Table 7 provides examples of medicines used to treat the indications covered by this submission.

Table 7: Examples of acquisition costs based on list prices.

Regimens	5 x 3ml cartridge	5 x 3ml pre-filled pen	3 x 1.5ml pre-filled pen/3 x3ml pre-filled pen	Approximate costs per patient (per annum)
Insulin degludec (Tresiba®▼) 100 units/ml 200 units/ml	£46.60 n/a	£46.60 n/a	n/a £55.92	£340–£681 £340–£680
Insulin glargine (Lantus®) 100 units/ml	£41.50	£41.50	n/a	£303–£606
Insulin glargine (Abasaglar®) 100units/ml	£35.28	£35.28	n/a	£258–£516
Insulin glargine (Toujeo®) 300units/ml	n/a	n/a	£33.13	£269–£538
Insulin detemir (Levemir®) 100units/ml	£42.00	£42.00	n/a	£307–£613
Insulin aspart (Novorapid®) 100 units/ml	£28.31	£30.60	n/a	£207–£447
NPH insulin (Insulatard®) 100 units/ml	£22.90	£20.40	n/a	£149–£334
NPH insulin (Humulin I®) 100 units/ml	£19.08	£21.70	n/a	£139–£317
NPH insulin (Insuman Basal®) 100 units/ml	£17.50	£19.80	n/a	£128–£289
Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of July 2016. Assumed dosing of 30 to 60 units daily. Costs of needles and disposables excluded. This table does not imply therapeutic equivalence of medicines or doses.				

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, insulin degludec (Tresiba®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation or by healthcare professionals with a special interest in diabetes mellitus.

The company do not anticipate that insulin degludec (Tresiba®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company has also identified additional on-going insulin degludec phase III studies that may provide additional evidence within the next 12 months[1]:

- Study NN1250-3995: A 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 (SWITCH 1)[50].
- Study NN1250-3998: A trial comparing the safety and efficacy of insulin degludec and insulin glargine, with or without OADs in subjects with type 2 diabetes (SWITCH 2)[51].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 12 and 13 May 2016.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Glycosylated haemoglobin (HbA_{1c})

This reflects the blood glucose level of a patient, where a higher HbA_{1c} level means more glucose has been present in the blood in the preceding few months[52,53]. Previously, HbA_{1c} results were reported as a percentage; however, from October 2011, laboratories in the UK switched to reporting results using new HbA_{1c} units, mmol/mol[53] (see Table 8).

Table 8. Comparison of HbA_{1c} results[53].

HbA_{1c} (%)	HbA_{1c} (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75

Treat-to-target

In treat-to-target studies, the insulin dose is adjusted for each individual patient with the aim of achieving identical glycaemic targets[19]. In such studies, any between treatment differences are therefore detected via other parameters, for example the rate of hypoglycaemia[1].

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