2\textsuperscript{nd} Re-submission

insulin degludec (Tresiba\textsuperscript{®}) 100units/mL solution for injection in pre-filled pen or cartridge and 200units/mL solution for injection in pre-filled pen

SMC No. (856/13)

Novo Nordisk Ltd.

08 July 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a second resubmission

insulin degludec (Tresiba\textsuperscript{®}) is accepted for use within NHS Scotland.

**Indication under review:** treatment of diabetes mellitus in adults.

In three phase III studies in adults with type 1 diabetes mellitus, and five phase III studies in adults with type 2 diabetes mellitus, insulin degludec was non-inferior to other long-acting insulin analogues, assessed by the mean change in glycosylated haemoglobin (HbA1c).

Insulin degludec is also indicated for the treatment of diabetes mellitus in adolescents and children from the age of 1 year. The holder of the marketing authorisation has not made a submission to SMC regarding this indication and as a result SMC cannot recommend its use within NHS Scotland.

Overleaf is the detailed advice on this product.

**Chairman,**
Scottish Medicines Consortium
**Indication**
Treatment of diabetes mellitus in adults.

**Dosing Information**
By subcutaneous injection (into the thigh, upper arm or abdominal wall) once daily at any time of day (but preferably at the same time each day), with a minimum interval of eight hours between doses. One unit of insulin degludec corresponds to one international unit of human insulin. It should be dosed in accordance with the individual patient’s requirements to optimise glycaemic control based on fasting plasma glucose. In patients with type 2 diabetes mellitus, insulin degludec can be administered alone or in combination with oral antidiabetic medicines, glucagon-like peptide-1 (GLP-1) receptor agonists and bolus insulin. In type 1 diabetes mellitus, it must be combined with a short-/rapid-acting insulin to cover mealtime requirements. Dose adjustment may be necessary if increased physical activity is undertaken, usual diet is changed or during concomitant illness. In patients with type 2 diabetes mellitus the starting dose is 10 units per day. In patients transferring from other basal insulins the conversion is one unit to one unit, although in those with type 1 diabetes mellitus transferring from twice daily basal insulin or having HbA1c <8.0% (<64mmol/mol), the dose at transfer should be determined on an individual basis.

**Product availability date**
21 January 2013

**Summary of evidence on comparative efficacy**
Insulin degludec is the third long-acting human insulin analogue licensed for treating diabetes. On subcutaneous (SC) injection, insulin degludec forms a depot of soluble multihexamers, which allow insulin to be slowly and continuously absorbed into the circulation. It has a long, flat time-action profile with a terminal half-life of over 25 hours and duration of action of over 40 hours.

This second resubmission for insulin degludec relates to the treatment of diabetes mellitus in adults (≥18 years) only. Since the initial submission, the license has been extended to allow use in adolescents and children aged over 1 year. In the absence of a submission, SMC issued advice in May 2015, advising that insulin degludec is not recommended for use in these patients.

Three similar, randomised, open-label, phase III studies (3583, 3585 and 3770) recruited adults diagnosed with type 1 diabetes mellitus (for at least a year) who had been treated with a basal-bolus regimen and had glycosylated haemoglobin (HbA1c) <10% (<86mmol/mol) and body mass index (BMI) ≤35kg/m². Patients were randomised to insulin degludec SC injection once daily (with the evening meal in studies 3583 and 3770, and between the evening meal and bedtime in study 3585) or,

- in study 3583, to insulin glargine SC injection once daily (at any time of the day), or
- in study 3585, to insulin detemir SC injection once daily (between evening meal and bedtime), or
- in study 3770, to insulin glargine SC injection once daily (at anytime of the day) or to insulin degludec SC injection by forced flexible (FF) dosing interval (in the morning on Monday, Wednesday and Friday and in the evening on the other days of the week)
Except for the FF treatment arm, the dosing interval was 24 hours. All patients received insulin aspart SC injection immediately before meals. Insulin doses were adjusted to achieve fasting plasma glucose (FPG) of 5mmol/L while avoiding hypoglycaemia, and investigators were recommended to focus on optimising the basal insulin dose first. Treatment continued for 52 weeks in study 3583, and for 26 weeks in the other studies.4-12

In all three studies, the primary outcome was the mean change in HbA1c from baseline to end of treatment. This was assessed in the full analysis population, which included all randomised patients. The studies were designed to demonstrate non-inferiority, with a pre-specified margin of 0.4%. Results detailed in Table 1 indicate that non-inferiority was demonstrated for insulin degludec compared with insulin glargine and insulin detemir in studies 3583 and 3585, respectively. This was also demonstrated in study 3770 for insulin degludec FF compared with insulin glargine and insulin degludec at a 24-hour dosing interval.4-12

Four similar, randomised, open-label, phase III studies (3579, 3672, 3586 and 3668) recruited adults diagnosed with type 2 diabetes mellitus (for at least six months) who had an HbA1c between 7% (53mmol/mol) and 10% (86mmol/mol) or, in study 3668, between 7% and 11% (97mmol/mol) for insulin-naïve patients. Study was 3668 was the only one that permitted inclusion of patients who were not insulin-naïve. A further similar study (3582) only recruited adults previously treated with insulin. Patients were randomised to insulin degludec SC injection once daily (with evening meal, except study 3586, in which it was given between the evening meal and bedtime) or insulin glargine SC injection once daily (at any time of the day). Study 3668 also included an insulin degludec SC FF dosing interval group. Basal insulin doses were adjusted to achieve FPG 5mmol/L while avoiding hypoglycaemia. In all studies, patients received additional therapy with oral anti-diabetic drugs (OADs) that were identical between treatment groups (basal-OAD regimen), except in study 3582, where patients received bolus insulin aspart SC with meals and continued previously prescribed OADs (basal-bolus regimen). Treatment was continued for 52 weeks in study 3579 and 3582, and for 26 weeks in the other studies. The primary outcomes and non-inferiority margins were identical to the type 1 diabetes studies. Results detailed in Table 1 indicate that insulin degludec was non-inferior to insulin glargine.4,6,7,13-22

Table 1: Change in HbA1c from baseline to end of treatment4-22

<table>
<thead>
<tr>
<th>Study</th>
<th>Insulin Degludec</th>
<th>Comparator</th>
<th>Difference** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Insulin</td>
<td>HbA1c*</td>
</tr>
<tr>
<td>Type 1 diabetes (basal-bolus regimen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3583</td>
<td>472 Degludec -0.36 157 Glargine -0.34</td>
<td>-0.01 (-0.14 to 0.11)</td>
<td></td>
</tr>
<tr>
<td>3585</td>
<td>302 Degludec -0.71 153 Detemir -0.61</td>
<td>-0.09 (-0.23 to 0.05)</td>
<td></td>
</tr>
<tr>
<td>3770</td>
<td>164 Degludec FF -0.40 164 Glargine -0.57</td>
<td>0.17 (0.04 to 0.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>165 Degludec -0.41</td>
<td>0.01 (-0.13 to 0.14)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes (basal-OAD regimen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3579</td>
<td>773 Degludec -1.06 257 Glargine -1.15</td>
<td>0.09 (-0.04 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>3672</td>
<td>228 Degludec -1.18 229 Glargine -1.22</td>
<td>0.04 (-0.11 to 0.19)</td>
<td></td>
</tr>
<tr>
<td>3586</td>
<td>289 Degludec -1.42 146 Glargine -1.52</td>
<td>0.11 (-0.03 to 0.24)</td>
<td></td>
</tr>
<tr>
<td>3668</td>
<td>229 Degludec FF -1.17 230 Glargine -1.21</td>
<td>0.04 (-0.12 to 0.20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>228 Degludec -1.03</td>
<td>-0.13 (-0.29 to 0.03)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes (basal-bolus regimen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3582</td>
<td>744 Degludec -1.10 248 Glargine -1.18</td>
<td>0.08 (-0.05 to 0.21)</td>
<td></td>
</tr>
</tbody>
</table>
*Least squares mean change in HbA1c (%) from baseline to end of treatment. **Treatment difference (insulin degludec minus comparator) for change in HbA1c (%) from baseline to end of treatment. n = number of patients. OAD = oral anti-diabetic drug. FF = forced flexible dosing interval. CI = confidence interval.

Real-world evidence was presented to supplement the randomised-controlled study data for insulin degludec. A retrospective case series analysis was conducted at a single centre in the UK to assess the value of switching patients with treatment-limiting problems on their existing insulin regimes to insulin degludec. Records from the first consecutive 51 patients (type 1 diabetes n=35; type 2 diabetes n=16) who had switched from insulin glargine or insulin detemir to insulin degludec were reviewed for up to 37 weeks (mean 25.5±6.0 weeks). Interim results demonstrated reductions in HbA1c and patient-reported hypoglycemic events. In Sweden, a prospective, open-label, single-arm, observational, clinical follow-up was conducted on consecutive patients with type 1 diabetes who switched from insulin glargine (n=216), insulin detemir (n=131), neutral protamine Hagedorn insulin (n=5) or continuous subcutaneous insulin infusion (n=5) to insulin degludec. The median time to follow-up was 20 weeks. The results demonstrated significant reductions from baseline in HbA1c, self-reported hypoglycemic events and nocturnal hypoglycemic events.

Other data were also assessed but remain commercially confidential.*

### Summary of evidence on comparative safety

The overall adverse event profile is typical of an insulin preparation, with hypoglycaemia being one of the main adverse events. The studies assessed confirmed hypoglycaemia, which could be an episode of severe hypoglycaemia as defined by the American Diabetic Association (ADA) (ie requiring assistance from another person to actively administer carbohydrate, glucagon or other resuscitative actions), or a minor hypoglycaemia episode, defined as plasma glucose <3.1mmol/L. There were no significant differences between insulin degludec and insulin glargine or insulin detemir in rates of overall confirmed hypoglycaemia in any of the studies, except study 3582 (basal-bolus) which showed significant reductions with insulin degludec compared with insulin glargine. Results are presented in table 2. When nocturnal hypoglycaemia was defined as confirmed hypoglycaemia occurring between midnight and 6am, significantly lower rates were reported for insulin degludec versus comparator in the type 1 diabetes studies and in two of the type 2 diabetes studies (3579 and 3582). However, in additional analyses of the type 1 studies when the nocturnal period was defined as 10pm to 6am or midnight to 8am, the advantage of insulin degludec over the comparator was not observed in either scenario.
Table 2: Confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Rate*</th>
<th>RR (95% CI)</th>
<th>Rate*</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hypoglycaemia</td>
<td>Nocturnal Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>Nocturnal Hypoglycaemia</td>
</tr>
<tr>
<td>3583</td>
<td>Degludec</td>
<td>4254</td>
<td>1.07 (0.89; 1.28)</td>
<td>441</td>
<td>0.75 (0.59; 0.96)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>4018</td>
<td></td>
<td>586</td>
<td></td>
</tr>
<tr>
<td>3585</td>
<td>Degludec</td>
<td>4583</td>
<td>0.98 (0.80; 1.20)</td>
<td>414</td>
<td>0.66 (0.49; 0.88)</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>4569</td>
<td></td>
<td>594</td>
<td></td>
</tr>
<tr>
<td>3770</td>
<td>Degludec FF</td>
<td>8238</td>
<td>1.03 (0.85; 1.26)</td>
<td>623</td>
<td>0.60 (0.44; 0.82)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>7973</td>
<td></td>
<td>996</td>
<td></td>
</tr>
<tr>
<td>3579</td>
<td>Degludec</td>
<td>152</td>
<td>0.82 (0.64; 1.04)</td>
<td>25</td>
<td>0.64 (0.42; 0.98)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>185</td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>3672</td>
<td>Degludec</td>
<td>122</td>
<td>0.86 (0.58; 1.28)</td>
<td>18</td>
<td>0.64 (0.30; 1.37)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>142</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>3586</td>
<td>Degludec</td>
<td>298</td>
<td>0.82 (0.60; 1.11)</td>
<td>78</td>
<td>0.62 (0.38; 1.04)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>370</td>
<td></td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>3668</td>
<td>Degludec FF</td>
<td>364</td>
<td>1.03 (0.75; 1.40)</td>
<td>63</td>
<td>0.77 (0.44; 1.35)</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>348</td>
<td></td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

* Event rate per 100 patient-years exposure. RR = rate ratio insulin degludec/comparator. OAD = oral antidiabetic drug. # = comparison of insulin degludec FF/degludec 24-hour dose interval. FF = forced flexible dosing interval. CI = confidence interval.

Meta-analyses were presented that included data from groups given either insulin degludec or insulin glargine at 24-hour dosing intervals (ie excluding data from insulin degludec FF groups in studies 3770 and 3668), with the meta-analysis in type 2 diabetes excluding patients from study 3668 who were not insulin-naïve patients. In type 1 diabetes, there were no significant differences between insulin degludec and insulin glargine for severe hypoglycaemia, confirmed hypoglycaemia or confirmed nocturnal hypoglycaemia (confirmed hypoglycaemia occurring between midnight and 6am). In the analyses of insulin-naïve patients with type 2 diabetes on a basal-OAD regimen, insulin degludec, compared with insulin glargine, significantly reduced rates of severe hypoglycaemia (rate ratio 0.14 [95% CI: 0.03 to 0.70]), confirmed hypoglycaemia (rate ratio 0.83 [95% CI: 0.70 to 0.98]), and confirmed nocturnal hypoglycaemia (0.64 [95% CI: 0.48 to 0.86]). In the type 2 diabetes basal-bolus regimen (study 3582), insulin degludec, compared with insulin glargine, significantly reduced rates of confirmed hypoglycaemia (rate ratio 0.82 [95% CI: 0.69 to 0.99]) and nocturnal hypoglycaemia (0.75 [95% CI: 0.58 to 0.99]), but the result for severe hypoglycaemia was non-significant.25,26 Similar results were obtained from another meta-analysis in which three mutually exclusive groups were defined (non-severe nocturnal, non-severe daytime and severe hypoglycaemia). In this analysis, significantly reduced rates of non-severe nocturnal hypoglycaemia were demonstrated for insulin degludec versus insulin glargine across all studies (rate ratio 0.83 [95% CI: 0.69 to 0.99], 0.64 [95% CI: 0.47 to 0.86] and 0.75 [95% CI: 0.57 to 0.98] for the type 1, type 2 basal-OAD and type 2 basal-bolus studies, respectively).27 It should, however, be noted that some of the CIs in the meta-analyses were close to overlapping 1, suggesting borderline significance.

During the US regulatory review, meta-analyses were presented of relative event rates of nocturnal hypoglycaemia with insulin degludec versus insulin glargine or insulin detemir. For confirmed nocturnal hypoglycaemia in the type 1 diabetes studies (3583, 3585, 3770), there was a rate ratio of 0.85 (95% C: 0.68 to 1.06); when two hours were added to the nocturnal period, the result remained non-significant at 1.05 (95% CI: 0.33 to 3.35). In the type 2 diabetes studies (3579, 3672, 3586, 3668, 3582), there was a significant rate ratio of 0.69 (95% CI: 0.59
to 0.81), and when two hours were added to the nocturnal period, the rate ratio became non-significant at 0.89 (95% CI: 0.47 to 1.72).\(^{28}\)

A post-hoc meta-analysis investigated the consistency of results for the rate of nocturnal hypoglycaemia with insulin degludec versus insulin glargine using the following differing definitions: nocturnal confirmed hypoglycaemia (plasma glucose <3.1mmol/L and severe episodes and occurring between 00:01 and 05:59, 21:59 and 05:59, and 00:01 and 07:59); nocturnal confirmed symptomatic hypoglycaemia (plasma glucose <3.1mmol/L and severe episodes and symptoms and occurring between 00:01 and 05:59); nocturnal ADA documented symptomatic hypoglycaemia (plasma glucose <3.9mmol/L and severe episodes occurring between 00:01 and 05:59). For all definitions across all time periods throughout the entire core study period, the risk of nocturnal hypoglycaemia was not significantly different for insulin degludec versus insulin glargine in the type 1 diabetes studies (3583, 3770), and the risk of nocturnal hypoglycaemia was significantly lower for insulin degludec versus insulin glargine in the type 2 diabetes studies (basal-OAD 3579, 3672, 3586; basal-bolus 3582), except for the time period 00:01 to 07:59 in the type 2 diabetes basal-OAD studies.\(^{29}\)

Mean body weight increased from baseline to end of study in all groups receiving an insulin, with no significant differences between groups, except in study 3585, where insulin degludec was associated with a significantly greater least squares mean weight increase than insulin detemir (1.5kg versus 0.4kg).\(^{6}\)

A meta-analysis of 16 phase III studies (excluding extension studies) of insulin degludec and insulin degludec/aspart for major adverse cardiovascular events (MACE), which included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and unstable angina was based on 80 cases and approximately 5,444 patient-years of exposure. The analysis indicated that the hazard ratio for degludec products over comparators was 1.1 (95% CI: 0.68 to 1.77). An update to this analysis (including data from ongoing extension studies) had 142 cases and approximately 7,716 patient-years of exposure. The hazard ratio for degludec products over comparators was 1.3 (95% CI: 0.88 to 1.93).\(^{6}\)

Other data were also assessed but remain commercially confidential.*

### Summary of clinical effectiveness issues

In the pivotal studies, insulin degludec was non-inferior to insulin glargine and insulin detemir in type 1 diabetes and was non-inferior to insulin glargine in type 2 diabetes, assessed by the primary outcome, mean change in HbA1c. HbA1c is the most widely accepted measure of long-term glycaemic control, and a reduction is associated with a reduced risk of microvascular and macrovascular complications.\(^{30}\) HbA1c results in the UK are now reported as mmol/mol rather than as a percentage. The HbA1c target of 6.5% to 7.5% or less (reference range 4.0% to 6.0%), is equivalent to 48mmol/mol to 59mmol/mol or less in the new units (reference range 20mmol/mol to 42mmol/mol).\(^{31}\)

There are issues with the evidence-base for the suggested advantage of insulin degludec over insulin glargine for confirmed hypoglycaemia and nocturnal hypoglycaemia:

- The effect on confirmed hypoglycaemia was not consistent across the types of diabetes. Meta-analyses indicated that insulin degludec, compared with other long-acting insulin analogues, was associated with a numerically higher rate of hypoglycaemia in type 1 diabetes, but a significantly lower rate in type 2 diabetes.
• The definition of confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia included asymptomatic measures of low blood glucose.

• The advantage of insulin degludec over other long-acting insulin analogues for confirmed nocturnal hypoglycaemia (between midnight and 6am) in the type 1 diabetes studies and the meta-analyses disappears when the nocturnal time period is extended by two hours.

• The studies excluded patients who suffered recurrent severe hypoglycaemia or hypoglycaemic unawareness, which limits the applicability of results in those most at risk of hypoglycaemia.

Another issue is the potential to use insulin degludec in a regimen with variable intervals between doses, based on study 3770 in type 1 diabetes and 3668 in type 2 diabetes. Within these studies, there were no significant differences between insulin degludec FF (dosing interval varying between 8 and 40 hours) and insulin degludec once daily (fixed 24-hour dosing interval) in mean change from baseline to endpoint in HbA1c or in rates of confirmed hypoglycaemia and nocturnal hypoglycaemia, except in study 3770, where confirmed nocturnal hypoglycaemia was lower with the FF regimen, with a rate ratio of 0.63 (95% CI: 0.46 to 0.86).

Patients who had cardiovascular disease (including stroke, decompensated heart failure [NYHA III or IV], myocardial infarction, unstable angina, coronary artery bypass graft or angioplasty) and uncontrolled treated or severe untreated hypertension were excluded from the studies; this limits the applicability of the results to those patients most at risk of adverse cardiovascular effects.

There are no direct comparative data with insulin detemir in type 2 diabetes.

Real-world evidence supported the results of the randomised-controlled studies and demonstrated reductions in HbA1c and patient-reported hypoglycaemia, although the studies were of open-label, non-randomised design. The UK study was further limited by inclusion of only a small patient population and selection of patients who had specifically switched therapy due to treatment-limiting problems on their previous insulin regime, and the Swedish study was reliant upon patient recall for an estimate of hypoglycaemia and lacked any validated measurement of patient satisfaction.

Insulin degludec is available in two strengths, 100 units/mL and 200 units/mL, in two different pen devices. As health professionals are familiar with the availability of insulin preparations in a strength of 100 units/mL, there is a possibility that having two available strengths may lead to confusion. The company has issued a letter to healthcare professionals with a series of recommendations to reduce the risk of medication errors with insulin degludec.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing insulin degludec to insulin glargine for the treatment of diabetes mellitus in adults (≥18 years). Cost-effectiveness results were presented for three separate patient groups:

• type 1 diabetes (basal-bolus regimen)
• type 2 diabetes (basal-OAD regimen)
• type 2 diabetes (basal-bolus regimen)
A short term, 1 year economic model, was conducted for each patient group and captured the incremental costs and quality adjusted life years (QALYs) associated with treatment. The key clinical driver within the model was hypoglycaemic events. The model assumes there are no differences in HbA1c, as non inferiority was considered to have been demonstrated between treatments. SMC clinical experts have indicated that insulin glargine is the comparator most likely to be displaced in Scotland.

The relative hypoglycaemic event rates for insulin degludec used within the economic model were derived from published literature, including a meta-analysis, while the baseline hypoglycaemia rates for patients receiving insulin glargine were taken from the UK Hypoglycaemia Study Group (UKHSG). Within each patient group, hypoglycaemic events were stratified according to non-severe daytime, non-severe night time and severe events. Based on the analysis, insulin degludec was estimated to have a non-severe nocturnal rate ratio versus insulin glargine of 0.83 (95% CI: 0.69 to 0.99) for the type 1 diabetes basal-bolus regimen group. For the type 2 diabetes basal-OAD regimen group, insulin degludec was estimated to have a non-severe nocturnal and severe rate ratio of 0.64 (95% CI: 0.47 to 0.88) and 0.14 (95% CI: 0.03 to 0.70) versus insulin glargine. For the type 2 diabetes basal-bolus regimen group, insulin degludec was estimated to have a non-severe daytime and non-severe nocturnal rate ratio of 0.83 (95% CI: 0.69 to 0.99) and 0.75 (95% CI: 0.57 to 0.98) respectively.

Drug acquisition costs were included in the analysis as well as the cost associated with needles and hypoglycaemic events. For the type 1 diabetes basal-bolus regimen group, the cost of a severe hypoglycaemic event was estimated to be £160, while for both the type 2 diabetes basal-OAD regimen and type 2 diabetes basal bolus groups, the cost for a severe hypoglycaemia event was estimated to be £365. Monitoring costs associated with self measured blood glucose were not included as this was assumed to be the same for both treatments.

Disutility associated with hypoglycaemic events was derived from published literature and applied to the difference in hypoglycaemic event rates between treatments in order to estimate QALYs for each patient group. Disutilities were estimated to be 0.0041, 0.0067 and 0.0565, for non-severe daytime, non-severe nocturnal and severe hypoglycaemic events respectively. The base case results estimated by the company are shown in Table 1.

<table>
<thead>
<tr>
<th>Insulin degludec vs insulin glargine</th>
<th>Type 1 diabetes (basal-bolus regimen)</th>
<th>Type 2 diabetes (basal-OAD regimen)</th>
<th>Type 2 diabetes (basal-bolus regimen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental costs</td>
<td>£-40</td>
<td>£-27</td>
<td>£138</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.0044</td>
<td>0.0073</td>
<td>0.0084</td>
</tr>
<tr>
<td>ICER</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£16,351</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio

It should be noted that in the type 1 basal-bolus subgroup, insulin degludec is associated with lower drug costs compared to insulin glargine despite having a higher price per pack. This is due to differential dosing assumptions based on the meta-analysis i.e. 28.80 vs. 33.10 units per day for insulin degludec and insulin glargine respectively. Within the type 2 basal-OAD subgroup, savings were primarily a result of fewer severe hypoglycaemic events. The QALY gain is being driven by fewer hypoglycaemic events in both the type 1 diabetes and type 2 diabetes basal-OAD regimens. For the type 2 diabetes basal-bolus group, the incremental cost stems from the higher drug costs associated with insulin degludec due to a higher dose of
insulin degludec in this subgroup, while the incremental QALY gain is a result of fewer nocturnal and daytime non-severe hypoglycaemic events.

The company provided sensitivity analyses including one-way, two-way, scenario analysis and probabilistic sensitivity analysis. For the type 1 diabetes basal-bolus and type 2 diabetes basal-OAD regimen groups, results were relatively insensitive to a change in key variables such as using an alternative source for hypoglycaemia rates and hypoglycaemia disutility. In a scenario analysis conducted within the type 1 diabetes basal-bolus subgroup, insulin degludec remained cost saving versus insulin glargine when no hypoglycaemia benefit was assumed (savings of £38.54). The incremental saving was due to the different dose ratio applied from the meta-analysis where a lower dose was required with insulin degludec in this subgroup. For the type 2 basal-bolus regimen group, results were most sensitive to two-way parameter variations. When the price of insulin glargine is reduced by 15% and disutilities associated with hypoglycaemia events are derived from an alternative source, the ICER increases to £37,056.

Within the type 2 diabetes basal-bolus group, there is some uncertainty associated with the rate ratios for insulin degludec given the limitations with the clinical data noted above. In order to test uncertainty surrounding hypoglycaemia rates, the company provided sensitivity analysis assuming no hypoglycaemia benefit with insulin degludec. When no difference in hypoglycaemia was assumed between treatments, insulin degludec was estimated to have an incremental cost of £143 versus insulin glargine.

Despite some limitations, the economic case has been demonstrated.

<table>
<thead>
<tr>
<th>Summary of patient and public involvement</th>
</tr>
</thead>
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The following information reflects the views of the specified Patient Group.

- A submission was received from Diabetes UK Scotland, which is a registered charity.

- The patient group has received 1% pharmaceutical company funding in the past two years, including from the submitting company.

- Diabetes is not easy to live with and it has a big impact on the day to day lives of people with the condition, their carers and families. It is a progressive condition and it is often difficult for people to attain and maintain glycaemic targets. When poorly controlled, it can lead to complications such as blindness, amputation, renal disease and reduced life expectancy, often due to coronary heart disease and/or stroke.

- There are many treatments for diabetes all of which have potential benefits and side effects which may impact on the person living with diabetes (PLWD). Those who require multiple treatment regimens often find it confusing, which may lead to difficulties with concordance. Glycaemic control, avoidance of hypoglycaemia and weight gain/loss are all of major concern to PLWD.

- Insulin degludec offers a further treatment option to those requiring insulin therapy, which provides an extended duration of action and the ability to change the time of day when it can be administered, thus providing greater flexibility.
In March 2010, the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 116, Management of Diabetes: a national clinical guideline. The guideline was last updated in May 2014. It recommends that an intensified treatment regimen for adults with type 1 diabetes should include either regular human or rapid-acting insulin analogues. Basal insulin analogues are recommended in adults with type 1 diabetes who are experiencing severe or nocturnal hypoglycaemia and who are using an intensified insulin regimen. Adults with type 1 diabetes who are not experiencing severe or nocturnal hypoglycaemia may use basal analogues or isophane (NPH) insulin. In people with type 2 diabetes it is recommended that oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control. Once daily bedtime NPH insulin should be used when adding insulin to metformin and/or sulphonylurea therapy. Basal insulin analogues should be considered if there are concerns regarding hypoglycaemia risk.

In August 2015, the National Institute for Health and Care Excellence (NICE) published clinical guideline number 17, Type 1 diabetes in adults: diagnosis and management. The guideline recommends offering multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. As alternative basal insulin therapy for adults with type 1 diabetes the following can be considered:

- An existing insulin regimen being used by a person that is achieving their agreed targets.
- Once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person or once-daily insulin glargine if insulin detemir is not tolerated.

Other basal insulin regimens for adults with type 1 diabetes should only be considered if the regimens above do not deliver agreed targets. Rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, should be offered for mealtime insulin replacement. Routine use of rapid-acting insulin after meals is not recommended. If however an adult with type 1 diabetes has a strong preference for alternative mealtime insulin, it is recommended that health professionals offer the preferred treatment. With regards mixed insulin, a twice-daily human mixed insulin regimen for adults with type 1 diabetes can be considered if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. If an adult using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life, NICE recommends trialing a twice-daily analogue mixed insulin regimen. In terms of optimising insulin therapy, rather than changing a previously optimised insulin regimen in adults with erratic and unpredictable blood glucose control; consideration should be given to: injection technique, injection sites, self-monitoring skills, knowledge and self-management skills, nature of lifestyle, psychological and psychosocial difficulties, and possible organic causes such as gastroparesis.

In December 2015, NICE published clinical guideline number 28, Type 2 diabetes in adults: management, which recommends initiating insulin therapy from a choice of a number of insulin types and regimens. Adults should begin with human (NPH) insulin once or twice daily according to need. As an alternative, a long-acting insulin analogue (insulin detemir, insulin glargine) should be considered if: the person needs assistance from a carer or healthcare professional to inject insulin, and use of long-acting insulin analogues (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily; or the person’s lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes; or the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering
drugs. Switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin should be considered in people who do not reach their target HbA1c because of significant hypoglycaemia; or who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached; or who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting analogue were made; or who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. Adults who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) should be monitored for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). Those adults who are on pre-mixed (biphasic) insulin should be monitored for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate.

**Additional information: comparators**

Insulin glargine and insulin detemir.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tbody>
<tr>
<td>Insulin degludec</td>
<td>Dose according to requirements (eg 30 to 60 units per day) by once daily subcutaneous injection</td>
<td>339 to 678</td>
</tr>
<tr>
<td>Insulin detemir (Levemir®)</td>
<td>Dose according to requirements (eg 30 to 60 units per day) by once or twice daily subcutaneous injection</td>
<td>306 to 612</td>
</tr>
<tr>
<td>Insulin glargine (Lantus®)</td>
<td>Dose according to requirements (eg 30 to 60 units per day) by once daily subcutaneous injection</td>
<td>302 to 604</td>
</tr>
<tr>
<td>Insulin glargine (Toujeo®)</td>
<td>Dose according to requirements (eg 30 to 60 units per day) by once daily subcutaneous injection</td>
<td>268 to 536</td>
</tr>
<tr>
<td>Insulin glargine (Abasaglar® [biosimilar])</td>
<td>Dose according to requirements (eg 30 to 60 units per day) by once daily subcutaneous injection</td>
<td>257 to 514</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. The dose should be individualised according to individual patient requirements. An example dose range of 30 units to 60 units per day has been used based on average insulin doses across the studies of insulin degludec. Cost for insulin degludec taken from the company's submission; all other costs from MIMS online 02/05/16.

**Additional information: budget impact**

The submitting company estimated the population eligible for treatment to be 33,638 in all years with an estimated uptake rate of 7% in year 1, rising to 30% in year 5, and a discontinuation rate of 5% in all years. The gross impact of the medicines budget is expected to be £1.4m in year 1 and £6.4m in year 5. As other medicines were assumed to be displaced, the net budget impact is expected to result in savings of £29k in year 1, rising to £75k in year 5. (The company estimated that 71% of insulin degludec use will be from Type 1 diabetes (basal bolus) patients,
15% from Type 2 diabetes basal OAD patients, and 14% from Type 2 diabetes (basal bolus) patients.)
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Novo Nordisk Limited. Tresiba 100 units/mL Cartridge (Penfill). Summary of product characteristics. Date of revision of the text: 04/2015.

2. Novo Nordisk Limited. Tresiba 100 units/mL Pre-filled Pen (FlexTouch). Summary of product characteristics. Date of revision of the text: 04/2015.

3. Novo Nordisk Limited. Tresiba 200 units/mL Pre-filled Pen (FlexTouch). Summary of product characteristics. Date of revision of the text: 04/2015.


8. Commercial in Confidence*

9. Commercial in Confidence*


11. Commercial in Confidence*


14. Commercial in Confidence*

16. Commercial in Confidence*


18. Commercial in Confidence*


20. Commercial in Confidence*

21. Commercial in Confidence*


28. US Food and Drug Administration. Slides for meeting of the FDA Endocrinologic and Metabolic Drug Advisory Committee meeting on 8 November 2012.


This assessment is based on data submitted by the applicant company up to and including 17 June 2016.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal.*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Advice context:**

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.