Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

# insulin degludec (Tresiba®) 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

08 March 2013

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 full submission

**insulin degludec (Tresiba®)** is not recommended for use within NHS Scotland.

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

Insulin degludec is non-inferior to other long-acting insulin analogues for treatment of type 1 and type 2 diabetes mellitus in adults assessed via glycosylated haemoglobin (HbA1c) and it is superior to a dipeptidylpeptidase-4 inhibitor in type 2 diabetes mellitus.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

Treatment of diabetes mellitus in adults.

## Dosing Information

Insulin degludec should be administered by subcutaneous injection once daily at any time of the day, with a minimum interval of 8 hours between doses, but preferably at the same time each day. One unit of insulin degludec corresponds to one international unit of human insulin. It should be dosed in accordance with individual patient's requirements to optimise glycaemic control based on fasting plasma glucose. It can be administered alone or in combination with oral antidiabetic drugs or in combination with short-/rapid-acting insulin. In type 1 diabetes it must be combined with a short-/rapid-acting insulin to cover mealtime requirements. In people with type 2 diabetes the starting dose is 10units per day. In patients transferring from other basal insulins the conversion is one unit to one unit, although in people with type 1 diabetes transferring from twice daily basal insulin or having HbA1c <8.0%, 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 a long-acting human insulin analogue licensed for treatment of diabetes.[1] On subcutaneous 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. It has a duration of action of over 40 hours and is detectable in blood up to 96 hours after injection. The submitting company has identified three pathways in which this basal insulin would be used: in a basal-bolus regimen in people with type 1 or type 2 diabetes or in combination with oral antidiabetic drugs (OADs), within a basal-OAD regimen, in people with type 2 diabetes.

Three similar randomised, open-label phase III studies (3583, 3585 and 3770) recruited adults with type 1 diabetes for at least one year, who had been treated with a basal-bolus regimen and had glycosylated haemoglobin (HbA1c) less than 10% and body mass index (BMI) 35kg/$m^2$ or less. In these studies patients were randomised to insulin degludec subcutaneous (sc) injection once daily (with the evening meal in study 3583 and 3770 and between 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 once daily (between evening meal and bedtime) or,
- in study 3770, to insulin degludec sc forced flexible (FF) dosing interval (in the morning on Monday, Wednesday and Friday and in the evening on the other days of the week) or insulin glargine sc injection once daily (at anytime of the day).

Except for the FF treatment arm, the dosing interval was 24 hours. All patients received insulin aspart sc immediately before meals. Insulin doses were adjusted to achieve fasting plasma glucose (FPG) 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 26 weeks in the other studies.[2-7]

The primary outcome was mean change in HbA1c from baseline to end of treatment. This was assessed in the full analysis population, which included all randomised patients, via an analysis of covariance (ANCOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors and age and baseline HbA1c as covariates. The studies were designed to demonstrate non-inferiority, with a pre-specified margin of 0.4%. Results detailed in the table indicate that non-inferiority was demonstrated for insulin degludec compared to insulin glargine and insulin detemir in studies 3583 and 3585. This was also demonstrated for insulin degludec FF compared to insulin glargine and to insulin degludec 24-hour dosing interval in study 3770.[2-7]

**Table 1: Type 1 diabetes studies, change in HbA1c from baseline to end of treatment**[2-7]

| Study | Insulin Degludec | | | Comparator | | | Difference** |
|---|---|---|---|---|---|---|---|
| | N | | HbA1c* | N | | HbA1c* | (95% CI) |
| 3583 | 472 | Degludec | -0.36 | 157 | Glargine | -0.34 | -0.01 (-0.14 to 0.11) |
| 3585 | 302 | Degludec | -0.71 | 153 | Detemir | -0.61 | -0.09 (-0.23 to 0.05) |
| 3770 | 164 | Degludec FF | -0.40 | 164 | Glargine | -0.57 | 0.17 (0.04 to 0.30) |
| | | | | 165 | Degludec | -0.41 | 0.01 (-0.13 to 0.14) |

* = 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. FF = forced flexible dosing interval. CI = confidence interval.

Four similar randomised, open-label phase III studies (3579, 3672, 3586 and 3668) recruited adults with type 2 diabetes for at least 6 months who had HbA1c between 7% and 10% or, in study 3668, between 7% and 11% for insulin-naïve patients. The latter study was the only one that permitted inclusion of patients who were not insulin-naïve. A further similar study (3582) only recruited adults treated with insulin. Patients were randomised to insulin degludec sc injection once daily (with evening meal, except study 3586, between evening meal and bedtime) or insulin glargine sc injection once daily (at any time of the day). Study 3668 also included an insulin degludec FF group, as described in the type 1 studies. In another similar study (3580) insulin-naïve adults with type 2 diabetes for at least 6 months who had HbA1c between 7.5% and 11% were randomised to insulin degludec sc once daily (at any time of the day) or sitagliptin 100mg daily. Insulin doses were adjusted to achieve FPG 5mmol/L while avoiding hypoglycaemia. In all studies patients received additional therapy with OADs that was identical between treatment groups, except study 3582, where patients received bolus insulin aspart sc with meals plus optional OAD. Treatment was continued for 52 weeks in studies 3579 and 3582 and for 26 weeks in the other studies.[3,4, 8-15]

Except for the comparison to sitagliptin, all studies were designed to assess non-inferiority, with a pre-specified margin of 0.4%. The primary outcome and methods of analyses were identical to the type 1 diabetes studies. Results detailed in the table indicate that insulin degludec was non-inferior to insulin glargine in all non-inferiority studies and was superior to sitagliptin. [3,4, 8-15]

**Table 2: Type 2 diabetes studies change in HbA1c from baseline to end of treatment**[3,4, 8-15]

| Study | Insulin Degludec | | | Comparator | | | Difference** |
|---|---|---|---|---|---|---|---|
| | N | | HbA1c* | N | | HbA1c* | (95% CI) |
| 3579 | 773 | Degludec | -1.06 | 257 | Glargine | -1.15 | 0.09 (-0.04 to 0.22) |
| 3672 | 228 | Degludec | -1.18 | 229 | Glargine | -1.22 | 0.04 (-0.11 to 0.19) |
| 3586 | 289 | Degludec | -1.42 | 146 | Glargine | -1.52 | 0.11 (-0.03 to 0.24) |
| 3580 | 225 | Degludec | -1.52 | 222 | Sitagliptin | -1.09 | -0.43 (-0.61 to -0.24) |
| 3668 | 229 | Degludec FF | -1.17 | 230 | Glargine | -1.21 | 0.04 (-0.12 to 0.20) |
| | | | | 228 | Degludec | -1.03 | -0.13 (-0.29 to 0.03) |
| 3582 | 744 | Degludec | -1.10 | 248 | Glargine | -1.18 | 0.08 (-0.05 to 0.21) |

* = 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. FF dosing = forced flexible dosing interval. CI = confidence interval

Short form 36 (SF-36) data changed marginally during each study, with occasional significant differences between treatments, but no consistent effect noted in any domain across all studies. A meta-analysis of SF-36 data from three studies in type 2 diabetes that recruited insulin-naïve patients (3579, 3586, 3672) indicated significant differences (95% confidence interval (CI)) on 100-point scales in favour of insulin degludec compared to insulin glargine of 0.66 (0.04 to 1.28) for overall physical score, 1.1 (0.22 to 1.98) for bodily pain and 0.81 (0.03 to 1.59) for vitality.[16]

## 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) (i.e. requiring assistance from another person to actively administer carbohydrate, glucagons or other resuscitative actions) or a minor hypoglycaemia episode, defined as a measured plasma glucose less than 3.1mmol/L. As this could include asymptomatic measurements of low blood glucose the US regulatory authority requested additional analyses of ADA defined documented symptomatic hypoglycaemia, that is episodes during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose ≤3.9 mmol/L. Nocturnal hypoglycaemia was defined as hypoglycaemia occurring between midnight and 6am and all analyses were repeated for this period.[2-15]

Results of these analyses are detailed in the table and indicate that in type 1 diabetes there were similar rates of confirmed and symptomatic hypoglycaemia with insulin degludec compared to insulin glargine and to insulin detemir. With insulin degludec there were lower rates of nocturnal hypoglycaemia, with significance reported for these in analyses of confirmed nocturnal hypoglycaemia.[2-7] In type 2 diabetes there were no significant differences in confirmed hypoglycaemia between insulin degludec and insulin glargine within a basal-OAD regimen, but there was a significant increase compared to sitagliptin and a significant reduction was seen with insulin degludec compared to insulin glargine used in a basal-bolus regimen. Within basal-OAD regimens rates of nocturnal hypoglycaemia were lower with insulin degludec compared to insulin glargine, reported as significant for confirmed nocturnal hypoglycaemia in study 3579, but the rate was greater compared to sitagliptin. Rates of confirmed nocturnal hypoglycaemia with insulin degludec were significantly lower compared to insulin glargine used within a basal-bolus regimen. [3,4,8-15]

.**Table 3: hypoglycaemia and nocturnal hypoglycaemia**[3,4,7,11,12]

| | | Hypoglycaemia | | Nocturnal Hypoglycaemia | |
|---|---|---|---|---|---|
| | | **Confirmed** | **Symptomatic** | **Confirmed** | **Symptomatic** |
| **Study** | **Treatment** | **RR (95% CI)** | **RR** | **RR (95% CI)** | **RR** |
| **Type 1 diabetes (basal-bolus regimen)** | | | | | |
| 3583 | Degludec | 1.07 (0.89; 1.28) | 1.04 | 0.75 (0.59; 0.96) | 0.80 |
| | Glargine | | | | |
| 3585 | Degludec | 0.98 (0.80; 1.20) | 1.11 | 0.66 (0.49; 0.88) | 0.79 |
| | Detemir | | | | |
| 3770 | Degludec FF | 1.03 (0.85; 1.26) | 1.01 | 0.60 (0.44; 0.82) | 0.69 |
| | Glargine | | | | |
| **Type 2 diabetes (basal-OAD regimen)** | | | | | |
| 3579 | Degludec | 0.82 (0.64; 1.04) | 1.08 | 0.64 (0.42; 0.98) | 0.70 |
| | Glargine | | | | |
| 3672 | Degludec | 0.86 (0.58; 1.28) | 0.93 | 0.64 (0.30; 1.37) | 0.78 |
| | Glargine | | | | |
| 3586 | Degludec | 0.82 (0.60; 1.11) | 1.08 | 0.62 (0.38; 1.04) | 0.88 |
| | Glargine | | | | |
| 3580 | Degludec | 3.81 (2.40; 6.05) | 3.6 | 1.93 (0.90; 4.10) | 3.42 |
| | Sitagliptin | | | | |
| 3668 | Degludec FF | 1.03 (0.75; 1.40) | 1.04 | 0.77 (0.44; 1.35) | 0.87 |
| | Glargine | | | | |
| **Type 2 diabetes (basal-bolus regimen)** | | | | | |
| 3582 | Degludec | 0.82 (0.69; 0.99) | 0.88 | 0.75 (0.58; 0.99) | 0.73 |
| | Glargine | | | | |

RR = rate ratio insulin degludec/comparator; OAD = oral antidiabetic drug.

Meta-analyses were presented that included data from groups given either insulin degludec or insulin glargine at 24-hour dosing intervals (i.e. excluding data from insulin degludec FF groups in studies 3770 and 3668), with the meta-analysis in type 2 diabetes insulin-naïve basal-OAD also excluding insulin-naïve patients from study 3668. These analyses used a negative binomial regression model adjusted for study, diabetes type, antidiabetic therapy at screening, sex, geographical region and age. In type 1 diabetes there were no significant differences between insulin degludec and insulin glargine for severe hypoglycaemia and confirmed hypoglycaemia. For confirmed nocturnal hypoglycaemia the difference between insulin degludec and insulin glargine was of borderline significance. In contrast for insulin-naïve patients with type 2 diabetes on a basal-OAD regimen insulin degludec, compared to insulin glargine, was associated with significantly reduced rates of severe hypoglycaemia confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia. The results of study 3582 were presented again in this context to indicate that in type 2 diabetes within a basal-bolus regimen insulin degludec, compared to insulin glargine, was associated with significantly reduced rates of confirmed hypoglycaemia and nocturnal hypoglycaemia but non-significant for severe hypoglycaemia.[17,18]

**Table 4: Meta-analysis of severe, confirmed hypoglycaemia and confirmed nocturnal hypoglycaemia.** [4,17,18]

| Estimated rate ratio degludec / glargine (95% CI) | Type 1 diabetes (basal-bolus) | Type 2 diabetes, insulin naive (basal-OAD) | Type 2 diabetes (basal-bolus) |
|---|---|---|---|
| **Studies in analysis** | **3538, 3770** | **3579, 3672, 3586** | **3582** |
| Severe hypoglycaemia | 1.12 (0.68 to 1.86) | 0.14 (0.03 to 0.70) | 1.14 (0.06 to 2.17) |
| Hypoglycaemia | 1.10 (0.96 to 1.26) | 0.83 (0.70 to 0.98) | 0.82 (0.69 to 0.99) |
| Nocturnal hypoglycaemia | 0.83 (0.69 to 1.00) | 0.64 (0.48 to 0.86) | 0.75 (0.58 to 0.99) |

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 (LS) mean weight increase than insulin detemir: 1.5kg versus 0.4kg. In study 3580 insulin degludec was associated with a significantly greater LS mean weight change from baseline compared to sitagliptin: 2.7kg versus -0.06kg.[3]

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 MI, non-fatal stroke and unstable angina was based on 80 cases and approximately 5,444 patient years of exposure. This 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). This has been identified as a cardiovascular safety signal that requires monitoring and investigation.[3]

*Other data were also assessed but remain commercially confidential.**

## Summary of clinical effectiveness issues

In the pivotal studies for control of diabetes, assessed via changes in HbA1c, insulin degludec was non-inferior to insulin glargine and insulin detemir in type 1 diabetes and was non-inferior to insulin glargine and superior to sitagliptin in type 2 diabetes.

The primary outcome measure used in the studies was the change in HbA1c. HbA1c is the most widely accepted measure of long-term glycaemic control, and lowering HbA1c is associated with a reduction in the risk of microvascular and macrovascular complications of diabetes. The way in which HbA1c results are expressed in the UK has changed recently; results are now reported as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.5% are 48mmol/mol and 58mmol/mol in the new units, with the non-diabetic reference range of 4.0% to 6.0% being 20mmol/mol to 42mmol/mol.

A key issue is the suggested advantage of insulin degludec over insulin glargine (both dosed at 24-hour intervals) for confirmed hypoglycaemia. This was not consistently demonstrated across type of diabetes as meta-analyses indicated rates of confirmed hypoglycaemia were higher (although non-significant) with insulin degludec in type 1 diabetes, but were significantly lower in type 2 diabetes.[17] There were numerically lower rates of confirmed hypoglycaemia with insulin degludec in type 2 diabetes basal-OAD studies (except 3668), reaching significance in a meta-

analysis that included data from insulin-naïve patients, except those in 3668. In type 2 diabetes within a basal-bolus regimen (study 3582) confirmed hypoglycaemia was significantly lower with insulin degludec compared to insulin glargine.

The meta-analyses demonstrated an advantage for insulin degludec for confirmed nocturnal hypoglycaemia, where the nocturnal period is defined as midnight to 6am, with numerically lower rates in all studies, that reached significance in the type 1 diabetes studies and in two studies in type 2 diabetes (3579 and 3582). In all studies insulin degludec was administered in the evening but insulin glargine could be given at any time of the day. It is possible that differences in timing of injections may have biased hypoglycaemia rates across set time periods. Additional analyses of the studies in type 1 diabetes (3583, 3585 and 3770) requested by the US Food and Drug Administration (FDA) in which the nocturnal period was defined as 10pm to 6am or midnight to 8am indicated that the advantage of degludec over comparator disappears in both scenarios.[3]

The open-label design of the studies could have affected reporting of adverse events such as hypoglycaemia, quality of life data and other subjective outcomes. In addition, many people in the studies which recruited patients already receiving insulin were using the comparator at baseline. These people would be continuing with an established treatment and familiarity with it could have affected their conduct in the study and reporting of adverse events, quality of life and other subjective outcomes. Familiarity with the comparator may also have affected investigators' behaviour, e.g. physicians may have been more cautious in adjusting doses of a novel insulin compared to a commonly used insulin.

Where a significant advantage was seen for insulin degludec over insulin glargine (dosed at 24-hour intervals) for confirmed hypoglycaemia (3582) the difference in patient reporting rates was less than 2% and event rate was reduced by 2.5 episodes per patient year of exposure and for nocturnal hypoglycaemia (3583, 3585, 3579, 3582) the differences in patient reporting rates were less than 8% and event rates were reduced by less than 2 and 0.5 episodes per patient year of exposure in people with type 1 and type 2 diabetes, respectively. The clinical significance of these treatment effects is unknown.

The studies excluded people who suffered recurrent severe hypoglycaemia or hypoglycaemic unawareness and people 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. This limits the application of results to those groups most at risk of hypoglycaemia or adverse cardiovascular effects.[2-13]

There are no direct comparative data with isophane (NPH) insulin in type 1 or 2 diabetes or with insulin detemir in type 2 diabetes.

SMC clinical experts indicated that insulin degludec, as an insulin with an ultra-long duration of action, could potentially offer some advantages over existing insulins in specific patients. For example, in patients who fail to maintain glycaemic control overnight despite optimisation of medication regimens and in patients who require injections to be administered by a third party such as a carer. SMC clinical experts also noted that caution is needed until long-term outcome and safety data are available for insulin degludec.

Insulin degludec is available in two strengths, 100 units/ml and 200 units/ml, in the form of two distinct 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 this new strength 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.

*Other data were also assessed but remain commercially confidential.**

## Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of insulin degludec compared to insulin glargine in the following three patient groups:

- Type 1 diabetes using a basal-bolus regimen ($T1DM_{B/B}$)
- Type 2 diabetes using a basal oral therapy regimen ($T2DM_{BOT}$)
- Type 2 diabetes using a basal-bolus regimen ($T2DM_{B/B}$)

For each of these groups, a simple economic model was constructed to show the costs and outcomes over a one year time horizon, which was assumed to provide a snapshot of longer treatment durations. On the basis that the key clinical trials had shown insulin degludec to be non-inferior to insulin glargine in terms of HbA1c, the outcomes in the model were structured around hypoglycaemic event rates and the need for self-measured blood glucose monitoring (SMBG).

Relative rates of hypoglycaemic events for each patient group were taken from the meta-analysis of relevant clinical trials and applied to the rates of events with insulin glargine found in a study from the literature. This method was selected on the basis that event rates in clinical trials may not reflect the rates of hypoglycaemic events seen in clinical practice. It should be noted that only differences found to be statistically significant in the meta analysis were used in the model. The models applied a rate of 7 SMBG tests per week related to basal insulin for patients treated with insulin glargine compared to 4 tests per week for patients treated with insulin degludec. This was on the basis of a treatment algorithm for insulin glargine and a suggested algorithm for insulin degludec from clinical trial findings.

Two different approaches to measuring utility were used in the analysis. One mapped SF-36 data collected in the clinical trial to EQ-5D and one used published values to estimate disutility associated with the two events of interest (hypoglycaemic attacks and SMBG tests). The SF-36 approach resulted in a difference in utility in favour of insulin degludec of 0.005 per year for each patient. In the disutility approach, disutilities of 0.0041, 0.0067 and 0.0565 were applied for each non-severe daytime, non-severe nocturnal and severe hypoglycaemic event respectively. Additionally, a disutility of 0.0058 per year was assumed for each additional SMBG test per week, on the basis of findings from a published study using EQ-5D. The company also applied this SMBG testing disutility in the SF-36 model as it was asserted that the SF-36 data from the trials would not reflect the SMBG testing regime assumed in the model.

In terms of resource use, unit costs for tests, needles and medicines were taken from standard sources. The costs associated with hypoglycaemic events (minor or severe) were estimated on the basis of patient data collected in the clinical trial programme. The costs of the events varied across the 3 patient groups, with the cost of a severe hypoglycaemic event being more than twice as high in the $T2DM_{BOT}$ group due to higher rates of hospitalisation.

The base case results are shown in the tables below, for both methods used to estimate utilities.

**Incremental cost-effectiveness, SF-36 model**

| | **$T1DM_{B/B}$** | **$T2DM_{BOT}$** | **$T2DM_{B/B}$** |
|---|---|---|---|
| Incremental costs- degludec v glargine | 86.58 | 120.33 | 532.21 |
| Incremental quality adjusted life years (QALY) | 0.0224 | 0.0224 | 0.0224 |
| **Incremental cost effectiveness ratio (ICER) (£/QALY)** | **£3,865** | **£5,372** | **£23,759** |

**Incremental cost-effectiveness, hypoglycaemia disutility model**

| | **$T1DM_{B/B}$** | **$T2DM_{BOT}$** | **$T2DM_{B/B}$** |
|---|---|---|---|
| Incremental costs | 86.58 | 120.33 | 532.21 |
| Incremental QALYs | 0.0218 | 0.0247 | 0.0258 |
| **ICER (£/QALY)** | **£3,969** | **£4,875** | **£20,589** |

A good range of sensitivity analyses was presented. These highlighted that the results for all groups were most sensitive to the assumed reduced frequency of SMBG tests and the disutility associated with these tests. The resulting ICERs are summarised in the table below

| | **$T1DM_{B/B}$** | | **$T2DM_{BOT}$** | | **$T2DM_{B/B}$** | |
|---|---|---|---|---|---|---|
| | SF-36 model | Disutility model | SF-36 model | Disutility model | SF-36 model | Disutility model |
| No difference in SMBGs | £27,801 | £31,500 | £34,551 | £23,712 | £116,926 | £69,194 |
| 50% reduction in disutility with each SMBG | £6,320 | £6,603 | £8,783 | £7,528 | £38,847 | £31,034 |
| Removal of disutility associated with SMBGs | £ 17,316 | £19,620 | £24,067 | £16,516 | £106,441 | £62,989 |

The results also showed some sensitivity to the relative dosing of insulin dosing for all groups and to the costs associated with severe hypoglycaemic events and the use of the clinical trial hypoglycaemia rates in the case of the $T2DM_{BOT}$ group.

As these results show, a key driver of the cost-effectiveness of insulin degludec were the assumptions made regarding the reduced frequency of SMBG tests and the disutility associated with SMBG. SMC clinical experts have indicated that it may be unlikely that any difference in testing frequency would occur in clinical practice. The inclusion of disutility around SMBG

testing is a novel one in terms of previous submissions to SMC in the area of diabetes. Aside from this, there are some weaknesses in how the disutility estimate appears to have been derived. An additional concern was that the results of the exercise to map the SF-36 results from the trial produced a significant difference in utility in favour of insulin degludec. This was despite few of the SF-36 results showing a significant difference between treatments.

In response to the New Drug Committee's criticism of the likely reduction in SMBG testing, the company provided additional new analysis to show cost-effectiveness in three specific subgroups of patients in a scenario where SMBG test reductions were not assumed. The $T2DM_{B/B}$ results were not presented for the revised analyses. The results were as follows:

- Subgroup 1 (patients in whom hypoglycaemia is a problem)- ICERs of £26,770 and £21,847 for the SF-36 and disutility models respectively in T1DM and £3,576 per QALY in the $T2DM_{BOT}$ group. In the $T2DM_{BOT}$ group, if the cost of a severe hypoglycaemic attack was reduced to £450 (as per the other groups), the ICER rose to £5,748.
- Subgroup 2 (patients in need of twice daily insulin)- ICERs of £21,146 and £23,960 for the SF-36 and disutility models respectively in T1DM and £27,897 and £19,145, for the SF-36 and disutility models respectively for the $T2DM_{BOT}$ group.
- Subgroup 3 (patients who are unable to inject at the same time every day)- ICERs of £12,637 and £13,349 for the SF-36 and disutility models in the T1DM group and £15,705 and £13,003 respectively for the $T2DM_{BOT}$ group.

While the results for the three subgroups of patients are noted, a full range of sensitivity analyses around these new estimates was not provided. Given that some of the new ICERs are not insignificant, it would be important to assess the possible range around these estimates to take into account other variables that the base case ICERs were known to have been sensitive to e.g. the cost of hypoglycaemic events, the use of clinical trial event rates and the relative dosing of insulin degludec. Further, the company did not provide evidence to support the clinical outcomes from the trial being applicable to the subgroups proposed.

Given these weaknesses and uncertainties, the economic case has not been demonstrated.

*Other data were also assessed but remain commercially confidential.**

## Summary of patient and public involvement

A Patient Interest Group submission was received from Diabetes UK Scotland.

## Additional information: guidelines and protocols

In March 2012 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 116, Management of Diabetes: a national clinical guideline. This recommends basal insulin analogues 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 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.[19]

In July 2004 the National Institute for Health and Clinical Excellence (NICE) published clinical guideline number 15, Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. This recommends that in adults basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at meal times or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice daily (or more often) should be considered. Long-acting insulin analogues (insulin glargine) should be used when: nocturnal hypoglycaemia is a problem on isophane (NPH) insulin; morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood glucose control; or rapid-acting insulin analogues are used for meal-time blood glucose control.[20]

In 2008 NICE published clinical guideline number 66, Type 2 diabetes: national clinical guideline for management in primary and secondary care.[21] This recommends that when starting basal insulin therapy continue with metformin and the sulphonylurea (and acarbose, if used) and review the use of the sulphonylurea if hypoglycaemia occurs and when starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens) continue with metformin and initially continue the sulphonylurea, but review and discontinue if hypoglycaemia occurs. Other recommendations relating to insulin therapy (R49 to R55) have been updated in May 2009 by the clinical guideline number 87, Type 2 diabetes: the management of type 2 diabetes.[24] This recommends to initiate insulin therapy from a choice of a number of insulin types and regimens. Begin with human (NPH) insulin injected at bedtime or twice daily according to need. Consider, as an alternative, using long-acting insulin analogue (insulin detemir, insulin glargine) 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; or the person cannot use the device to inject NPH insulin. Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin 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.

## Additional information: comparators

Other long-acting insulins: isophane insulin (NPH), insulin detemir and insulin glargine. SMC has accepted insulin glargine and insulin detemir for restricted use, targeted at patients attempting to achieve better hypoglycaemic control or, for insulin glargine, at people who experience unacceptable rates of nocturnal hypoglycaemia.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|---|---|---|
| **Insulin degludec** | **dose according to requirements (e.g. 30 to 60 units per day) by once daily subcutaneous injection** | **525 to 1,049** |
| Insulin detemir | dose according to requirements (e.g. 30 to 60 units per day) by once or twice daily subcutaneous injection | 306 to 612 |
| Insulin glargine | dose according to requirements (e.g. 30 to 60 units per day) by once daily subcutaneous injection | 303 to 605 |
| Isophane insulin | dose according to requirements (e.g. 30 to 60 units per day) by once or several times daily subcutaneous injection | 82 to 164 |

Doses are for general comparison and do not imply therapeutic equivalence. Doses are individualised according to individual patient requirements. An example dose range of 30units to 60units per day has been used based on average insulin doses across the studies of insulin degludec. Costs from eVadis on 20.12.12

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 33,104 in year 1 rising to 41,986 in year 5 with an estimated uptake rate of 3% in year 1 and 15% in year 5 and a discontinuation rate of 10% in all years. The gross impact on the medicines budget was estimated to be £627k in year 1 and £3.975m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £373k in year 1 and £2.364m in year 5.

References

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


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2. Heller S, Buse J, Fisher M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379: 1489-97
3. US Food and Drug Administration. Briefing document for meeting of the FDA Endocrinologic and Metabolic Drug Advisory Committee meeting on 8 November 2012
4. Novo Nordisk. Briefing document for meeting of the FDA Endocrinologic and Metabolic Drug Advisory Committee meeting on 8 November 2012
5. Novo Nordisk. Clinical study report for 3583
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16. Freemantle N, Meneghini L, Christensen T et al. Insulin degludec improves health-related quality of life (SF-36) compared with insulin glargine in people with type 2 diabetes starting on basal insulin: a meta-analysis of phase 3a trials. Diabetic Medicine 2013; 30: 226-232
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19. Scottish Intercollegiate Guidelines Network (SIGN). Management of Diabetes: a national clinical guideline, March 2012
20. National Institute for Health and Clinical Excellence (NICE). Clinical guideline number 15, Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults, July 2004.
21. National Institute for Health and Clinical Excellence (NICE). Clinical guideline number 66, Type 2 diabetes: national clinical guideline for management in primary and secondary care, 2008.
22. National Institute for Health and Clinical Excellence (NICE). Clinical guideline number 87, Type 2 diabetes: the management of type 2 diabetes, May 2009

This assessment is based on data submitted by the applicant company up to and including 15 February, 2013.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.*