Type 1 diabetes: insulin degludec

Evidence summary
Published: 10 September 2013
nice.org.uk/guidance/esnm24

This advice replaces ESNM5.

Key points from the evidence

The content of this evidence summary was up-to-date in September 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

The long-acting insulin analogue, insulin degludec, is available in 2 strengths: 100 units/ml and 200 units/ml. It is non-inferior to insulin glargine in terms of glycaemic control in type 1 diabetes, with statistically significantly lower rates of nocturnal hypoglycaemia. Although there is one published 104 week study reporting some safety data, there are no published studies comparing insulin degludec with NPH (isophane) insulin and none that measure patient-oriented efficacy outcomes.
### Effectiveness
- Insulin degludec is non-inferior to insulin glargine for glycaemic control.
- Insulin degludec reduced HbA1c by between 0.1% points [1 mmol/mol] and 0.4% points [4 mmol/mol] from baseline (2 RCTs, up to 104 weeks).
- These reductions in HbA1c were non-inferior to insulin glargine.

### Safety
- The MHRA has issued advice to minimise the risk of medication errors associated with the higher strength 200 units/ml formulation.
- The dose-counter window of the pen device shows the number of units, irrespective of strength. Therefore, no dose conversion is needed.

### Patient factors
- Once daily, with flexibility in timing of administration. SmPC states that a minimum of 8 hours between injections should always be ensured.
- Similar tolerability to insulin glargine.
- Statistically significant reductions in nocturnal hypoglycaemia of between 1.4 and 4 episodes per patient per year with insulin degludec compared with insulin glargine (2 RCTs up to 104 weeks).

### Key points
Insulin degludec (Tresiba) is a long-acting insulin analogue that has been marketed in the UK for basal insulin therapy in adults (18 years or over) with type 1 or type 2 diabetes. It is available in 2 strengths: 100 units/ml and 200 units/ml. This evidence summary considers the use of insulin degludec in adults with type 1 diabetes. It supersedes an earlier evidence summary (ESNM5), published in November 2012. Another evidence summary considers its use in adults with type 2 diabetes.

This evidence summary is based on 2 randomised controlled trials (RCTs) in which insulin degludec was compared with insulin glargine (Heller et al. 2012 and Bode et al. 2013; and Mathieu et al. 2013).
Evidence from the 2 open-label RCTs indicates that insulin degludec is non-inferior to insulin glargine in terms of glycaemic control: both basal insulins reduced glycated haemoglobin (HbA1c) levels to a similar degree (as would be expected with a treat-to-target trial design). With regard to hypoglycaemia, insulin degludec statistically significantly reduced the rate of nocturnal hypoglycaemia compared with insulin glargine. However, the absolute difference in this rate was small (between 1.4 and 4 episodes per patient per year at up to 104 weeks) and the trials failed to find a difference in the rates of overall, daytime or severe hypoglycaemia. There are no published studies comparing insulin degludec with NPH (isophane) insulin and none that measure patient-oriented efficacy outcomes.

Insulin degludec is given once daily at any time of the day, preferably at the same time every day. On occasions when this is not possible, there can be some flexibility in the timing of insulin administration. The Summary of product Characteristics states that a minimum of 8 hours between injections should always be ensured.

Insulin degludec is the first insulin approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued advice to minimise the risk of medication errors associated with the 200 units/ml formulation. The dose-counter window of the pen device shows the number of units that will be injected, irrespective of strength. Therefore, no dose conversion is needed when transferring a person from one strength of insulin degludec to another.

Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15; which is currently being updated) recommends that basal insulin supply for adults should be provided by using NPH (isophane) insulin or a long-acting insulin analogue. Examples of NPH (isophane) insulin include Insulatard, Humulin I or Insuman Basal. NICE recommends that a long-acting insulin analogue should be used when:

- nocturnal hypoglycaemia is a problem on NPH (isophane) insulin
- morning hyperglycaemia on NPH (isophane) insulin results in difficult daytime blood glucose control
- rapid-acting insulin analogues are used for mealtime blood glucose control.

Insulin degludec will be included in the update of this guideline, the publication date of which is still to be confirmed.
Local decision makers will need to consider the evidence for insulin degludec in type 1 diabetes alongside that for other basal insulins. Individual patient factors and their experience of hypoglycaemia together with the higher cost of insulin degludec will need to be taken into account.

**Key evidence**


**Update**

The following information has become available since this ESNM was produced.

April 2015: High strength, fixed combination and biosimilar insulin products minimising the risk of medication error

The MHRA has issued advice on how to minimise the risk of medication errors with high strength, fixed combination or biosimilar insulin products. Insulin degludec is available in 2 strengths and as a fixed combination product with liraglutide. See the Drug Safety Update April 2015 for more information.

August 2015: Updated NICE guideline on type 1 diabetes published

The updated NICE guideline on type 1 diabetes in adults: diagnosis and management has now been published. The guideline does not give any specific recommendations on the use of insulin degludec in type 1 diabetes. See the NICE guideline for more information.
About this evidence summary

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Relevance to NICE guidance programmes

Insulin degludec for type 1 diabetes will be included in the update of the NICE clinical guideline on type 1 diabetes. The publication date for this guideline is to be confirmed.

Introduction

Type 1 diabetes is a long-term hormonal deficiency disorder treated with insulin replacement therapy. Over the long term, type 1 diabetes is associated with an increased risk of major complications and reduced life expectancy. Appropriate control of blood glucose, blood pressure and lipids, as well as lifestyle choices, aims to reduce these risks.

The NICE clinical guideline on the diagnosis and management of type 1 diabetes (which is currently being updated) recommends that adults with type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal wellbeing. Basal insulin supply should be provided by using NPH (isophane) insulin or a long-acting insulin analogue. Examples of NPH (isophane) insulin include Insulatard, Humulin I or Insuman Basal. The guideline refers specifically to the long-acting insulin analogue, insulin glargine. It does not mention insulin detemir or insulin degludec because these were not available when the guideline was produced.

The NICE clinical guideline advises that, for adults, maintaining an HbA\(_1c\) level below 59 mmol/mol (7.5%) is likely to minimise the risk of developing diabetic eye, kidney or nerve damage in the longer term. It also advises that approaching lower HbA\(_1c\) levels (for example, 48 mmol/mol [6.5%] or lower) may be of benefit where there is evidence of increased arterial risk (identified by a raised albumin excretion rate, features of the metabolic syndrome, or other arterial risk factors). However, as is also discussed in the guideline, tighter blood glucose control needs to be balanced against the risks of hypoglycaemia. See the NICE pathway on diabetes for more information, and also the Clinical Knowledge Summary on type 1 diabetes for a general overview of prescribing considerations.
Product overview

Drug action

Insulin degludec (Tresiba) is a long-acting insulin analogue given once daily as a subcutaneous injection for basal insulin therapy. It has a duration of action beyond 42 hours within the therapeutic dose range. On occasions when administration at the same time of the day is not possible, insulin degludec allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should always be ensured (Insulin degludec (Tresiba): summaries of product characteristics).

Licensed therapeutic indication

The licensed indication is treatment of diabetes mellitus in adults (Insulin degludec (Tresiba): summaries of product characteristics). This evidence summary covers only the use of once-daily insulin degludec, as a single preparation, in adults with type 1 diabetes. (A combination preparation containing both insulin degludec and insulin aspart has also been licensed but has not yet been marketed in the UK.)

Course and cost

Insulin degludec is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day. In type 1 diabetes mellitus, insulin degludec must be combined with short- or rapid-acting insulin to cover mealtime insulin requirements. It is dosed in accordance with the individual patient’s needs. On occasions when administration at the same time of the day is not possible, insulin degludec allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should always be ensured (Insulin degludec (Tresiba): summaries of product characteristics).

Insulin degludec is available in 2 strengths: 100 units/ml and 200 units/ml. The dose-counter window of the pen device shows the number of units that will be injected, irrespective of strength. Therefore, no dose conversion is needed when transferring a person from one strength of insulin degludec to another. This is the first insulin approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued advice to minimise the risk of medication errors associated with a 200 units/ml formulation (see the section on safety for more information; Drug Safety Update April 2013).
Insulin degludec (Tresiba) is available in packs of 5×3 ml cartridges of 300 units/cartridge (100 units/ml) compatible with the NovoPen at a cost of £72.00. It is also available in the FlexTouch pre-filled pen device as a 5×3 ml – 300 units/pen (100 units/ml) at a cost of £72.00 and a double-strength 3×3ml – 600 units/pen (200 units/ml) at a cost of £86.40. Costs are excluding VAT; taken from MIMS (July 2013).

Evidence review

This evidence review is based on the following phase III studies in adults with type 1 diabetes, which have been published in full:

- BEGIN Basal-Bolus Type 1 of insulin degludec compared with insulin glargine in adults with type 1 diabetes (Heller et al. 2012; see table 1 and Bode et al. 2013 [an extension to this study]).

- BEGIN Flex T1 of insulin degludec in a pre-specified flexible dosing schedule compared with insulin degludec or insulin glargine at the same time each day (Mathieu et al. 2013; see table 2)

Another phase III study comparing insulin degludec with insulin detemir in type 1 diabetes has been completed but not yet published (ClinicalTrials.gov Identifier: NCT01074268).

BEGIN Basal-Bolus Type 1 (Heller et al. 2012 and Bode et al. 2013)

- Design: open-label, non-inferiority, 52-week randomised controlled trial (RCT) with a 52-week extension. Allocation concealed.

- Population: 629 adults (18 years or over, across 79 sites in 6 countries) with type 1 diabetes (HbA1c 86 mmol/mol [10%] or less [median 61 mmol/mol; 7.7%] and body mass index 35 kg/m² or less [median 26 kg/m²]) who had been treated with basal-bolus insulin for at least a year.

- Intervention and comparison: once-daily subcutaneous insulin degludec 100 units/ml (given with the main evening meal) compared with once-daily subcutaneous insulin glargine 100 units/ml (given at the same time each day), both in combination with mealtime subcutaneous insulin aspart, in a treat-to-target approach. Basal and bolus insulin were titrated to aim for self-measured plasma glucose levels of between 3.9 mmol/l and less than 5.0 mmol/l before breakfast for basal insulin, and pre-prandially and at bedtime for bolus insulin.
Outcome: the primary outcome was non-inferiority of insulin degludec to insulin glargine, assessed as a reduction in HbA\(_1c\) from baseline after 52 weeks, with the intention-to-treat analysis. Secondary outcomes included change from baseline in fasting plasma glucose.

Table 1 Summary of BEGIN Basal-Bolus Type 1: Heller et al. (2012)

<table>
<thead>
<tr>
<th></th>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full analysis set(^a) (ITT group)</td>
<td>n=472</td>
<td>n=157</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: mean change in HbA(_1c) from baseline to week 52</td>
<td>-0.40% (SE 0.03) points from baseline of 7.7% (61 mmol/mol)</td>
<td>-0.39% (SE 0.07) points from baseline of 7.7% (61 mmol/mol)</td>
<td>Estimated treatment difference in the ITT group -0.01% points (95% CI -0.14 to 0.11; p&lt;0.0001 for 1-sided test of non-inferiority(^b) evaluated at the 2.5% level) Estimated treatment difference in the per-protocol analysis(^c) -0.01% points (95% CI -0.14 to 0.12)</td>
</tr>
<tr>
<td><strong>Selected secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean change in FPG from baseline to week 52</td>
<td>-1.3 mmol/l (SE 0.2)</td>
<td>-1.4 mmol/l (SE 0.4)</td>
<td>Estimated treatment difference -0.33 mmol/l (95% CI -1.03 to 0.36; p=0.35). No statistically significant difference</td>
</tr>
<tr>
<td>Mean change in SMPG before breakfast from baseline to week 52</td>
<td>From 8.6 mmol/l (SE 0.1) to 7.3 mmol/l (SE 0.1)</td>
<td>From 8.6 mmol/l (SE 0.2) to 7.8 mmol/l (SE 0.2)</td>
<td>Estimated treatment difference -0.55 mmol/l (95% CI -1.03 to -0.08; p=0.023)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety analysis set(^d)</td>
<td>n=472</td>
<td>n=154</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>N1 (N2)</td>
<td>N2 (N3)</td>
<td>Rate ratio (95% CI)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Participants with severe hypoglycaemia</strong> (needing assistance)</td>
<td>12% (58/472)</td>
<td>10% (16/154)</td>
<td>Estimated rate ratio 1.38 (0.72 to 2.64; p=0.34)</td>
</tr>
<tr>
<td><strong>Participants with overall confirmed hypoglycaemia</strong></td>
<td>96% (451/472)</td>
<td>95% (147/154)</td>
<td>Estimated rate ratio 1.07 (0.89 to 1.28; p=0.48)</td>
</tr>
<tr>
<td><strong>Participants with diurnal confirmed hypoglycaemia</strong></td>
<td>94% (444/472)</td>
<td>94% (145/154)</td>
<td>Estimated rate ratio 1.11 (0.91 to 1.34; p=0.30)</td>
</tr>
<tr>
<td><strong>Participants with nocturnal confirmed hypoglycaemia</strong></td>
<td>72% (341/472)</td>
<td>74% (114/154)</td>
<td>Estimated rate ratio 0.75 (0.59 to 0.96; p=0.021)</td>
</tr>
<tr>
<td><strong>Participants reporting serious adverse events</strong></td>
<td>10% (49/472)</td>
<td>11% (17/154)</td>
<td>Statistical significance not reported</td>
</tr>
<tr>
<td><strong>Mean weight gain</strong></td>
<td>1.8 kg (SE 0.2)</td>
<td>1.6 kg (SE 0.3)</td>
<td>Estimated treatment difference 0.18 kg (95% CI 0.54 to 0.91; p=0.62)</td>
</tr>
<tr>
<td><strong>Injection-site reactions</strong></td>
<td>3% (13/472)</td>
<td>5% (8/154)</td>
<td>Statistical significance not reported</td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; ITT, intention-to-treat; n, number of patients; PYE, patient-years of exposure; SE, standard error; SMPG, self-measured plasma glucose.

a All participants who were randomly assigned to treatment.

b Non-inferiority was confirmed if the upper limit of the 95% confidence interval of the treatment difference was 0.4% points (4.4 mmol/mol) or less, as recommended by regulatory guidelines.

c All participants who complied with all recruitment criteria, had at least 12 weeks’ exposure to treatment and had valid assessments of HbA1c at baseline and at or after 12 weeks of treatment (insulin degludec, n=448; insulin glargine, n=147).

d All participants randomised who were exposed to treatment.

e Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3.1 mmol/l or severe episodes needing assistance. Diurnal episodes occurred between 0600h and 0000h; nocturnal episodes between 0001h and 0559h.

BEGIN Flex T1 (Mathieu et al. 2013)

- Design: open-label, non-inferiority, 26-week RCT with a 26-week extension. Allocation concealed.

- Population: 493 adults (18 years or over, across 71 sites in 6 countries) with type 1 diabetes (HbA1c 86 mmol/mol [10%] or less [mean 61 mmol/mol; 7.7%] and body mass index 35 kg/m² or less) who had been treated with basal-bolus insulin for at least a year.

- Intervention and comparison: once-daily subcutaneous insulin degludec 100 units/ml given in a forced-flexible regimen (with a minimum of 8 hours and a maximum of 40 hours between doses) compared with once-daily subcutaneous insulin degludec 100 units/ml given with the evening meal or once-daily subcutaneous insulin glargine 100 units/ml given at the same time each day; all in combination with mealtime subcutaneous insulin aspart, in a treat-to-target approach. Basal insulin was titrated to aim for self-measured plasma glucose levels of between 4.0 mmol/l and 5.0 mmol/l before breakfast. Bolus insulin was titrated to a mean pre-meal self-measured plasma glucose level of less than 5.0 mmol/l.

- Outcome: the primary outcome was non-inferiority of insulin degludec in the forced-flexible regimen to insulin glargine, assessed as a change in HbA1c from baseline to week 26 with the intention-to-treat analysis. Secondary outcomes included change from baseline in fasting plasma glucose.
Table 2 Summary of BEGIN Flex T1: Mathieu et al. (2013)

<table>
<thead>
<tr>
<th></th>
<th>Insulin degludec flexible once-daily dosing</th>
<th>Insulin degludec once daily in the evening</th>
<th>Insulin glargine once daily</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full analysis set&lt;sup&gt;a&lt;/sup&gt; (ITT group)</td>
<td>n=164</td>
<td>n=165</td>
<td>n=164</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong> mean change in HbA&lt;sub&gt;1c&lt;/sub&gt; from baseline to week 26</td>
<td>−0.40% (SD 0.59) points from baseline of 7.7% (61 mmol/mol)</td>
<td>−0.41% (SD 0.71) points from baseline of 7.7% (61 mmol/mol)</td>
<td>−0.58% (SD 0.72) points from baseline of 7.7% (61 mmol/mol)</td>
<td>Estimated treatment difference between insulin degludec flexible dosing and insulin glargine in the ITT group 0.17% points (95% CI 0.04 to 0.30) confirms non-inferiority&lt;sup&gt;b&lt;/sup&gt; Estimated treatment difference between insulin degludec flexible dosing and insulin glargine in the per-protocol analysis&lt;sup&gt;c&lt;/sup&gt; 0.15% points (95% CI 0.01 to 0.29)</td>
</tr>
</tbody>
</table>

Selected secondary outcomes:
| Mean change in FPG from baseline to week 26 | -1.28 mmol/l (SD 5.03) | -2.54 mmol/l (SD 5.11) | -1.33 mmol/l (SD 5.21) | Estimated treatment difference between insulin degludec flexible dosing and insulin glargine −0.05 mmol/l (95% CI −0.85 to 0.76; not statistically significant) Estimated treatment difference between insulin degludec flexible dosing and insulin degludec once daily 0.95 mmol/l (95% CI 0.15 to 1.75; p=0.021) |
| Safety | Safety analysis set | n=164 | n=165 | n=161 | |
| Participants with severe hypoglycaemia (needing assistance) at week 26 | 10.4% (17/164) 0.3 per PYE | 12.7% (21/165) 0.4 per PYE | 9.9% (16/161) 0.5 per PYE | Estimated rate ratio between insulin degludec flexible dosing and insulin glargine 0.89 (95% CI 0.40 to 1.99; not statistically significant) |
| Participants with overall confirmed hypoglycaemia at week 26 | 93.9% (154/164) 82.4 per PYE | 99.4% (164/165) 88.3 per PYE | 96.9% (156/161) 79.7 per PYE | Estimated rate ratio between insulin degludec flexible dosing and insulin glargine 1.03 (95% CI 0.85 to 1.26; not statistically significant) |
| Participants with nocturnal confirmed hypoglycaemia at week 26 | 67.7% (111/164) 6.2 per PYE | 73.3% (121/165) 9.6 per PYE | 72.7% (117/161) 10.0 per PYE | Estimated rate ratio between insulin degludec flexible dosing and insulin glargine 0.60 (95% CI 0.44 to 0.82; p=0.001) Estimated rate ratio between insulin degludec flexible dosing and insulin degludec once daily 0.63 (95% CI 0.46 to 0.86; p=0.003) |
Participants reporting serious adverse events (week 0 to week 26)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage (Number)</th>
<th>Events per 100 PYE</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5% (9/164)</td>
<td>17 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
<tr>
<td>4.2% (7/165)</td>
<td>12 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
<tr>
<td>5.0% (8/161)</td>
<td>10 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
</tbody>
</table>

Mean weight gain (week 0 to week 26)

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight Gain (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5% (9/164)</td>
<td>1.2 kg (SD 3.5)</td>
</tr>
<tr>
<td>4.2% (7/165)</td>
<td>0.8 kg (SD 2.5)</td>
</tr>
<tr>
<td>5.0% (8/161)</td>
<td>1.6 kg (SD 3.7)</td>
</tr>
</tbody>
</table>

Injection-site reactions (week 0 to week 26)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage (Number)</th>
<th>Events per 100 PYE</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9% (8/164)</td>
<td>15 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
<tr>
<td>1.8% (3/165)</td>
<td>4 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
<tr>
<td>2.5% (4/161)</td>
<td>5 events</td>
<td>Statistical significance not reported</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; ITT, intention-to-treat; n, number of patients; PYE, patient-years of exposure; SD, standard deviation.

a All participants who were randomly assigned to treatment.

b Non-inferiority was confirmed if the upper limit of the 95% confidence interval of the treatment difference was 0.4% points (4.4 mmol/mol) or less, as recommended by regulatory guidelines.

c All participants who complied with all recruitment criteria, had at least 12 weeks' exposure to treatment and had valid assessments of HbA1c at baseline and at or after 12 weeks of treatment (insulin degludec flexible once-daily dosing n=138; insulin degludec once daily in the evening, n=139; insulin glargine, n=152).

d All participants randomised who were exposed to treatment.

e Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3.1 mmol/l or severe episodes needing assistance. Nocturnal episodes occurred between 0001h and 0559h.

f No statistical analysis was done on the results of the groups receiving insulin degludec once daily in the evening and those receiving insulin glargine once daily.

Clinical effectiveness

Two open-label RCTs compared insulin degludec with insulin glargine in people with type 1 diabetes who had been treated with basal-bolus insulin for at least a year. In BEGIN Basal-Bolus Type 1 (Heller et al. 2012), the primary outcome was non-inferiority of insulin degludec (given once daily in the evening) to insulin glargine (given once daily at the same time each day), assessed as a...
reduction in HbA\textsubscript{1c} levels from baseline to week 52. In BEGIN Flex T1 (Mathieu et al. 2013), the primary outcome was non-inferiority of insulin degludec (given in a flexible once-daily dosing regimen, with between 8 and 40 hours between doses) to insulin glargine (given once daily at the same time each day), assessed as a change in HbA\textsubscript{1c} levels from baseline to week 26.

Both RCTs found that insulin degludec was non-inferior to insulin glargine in terms of glycaemic control. Both basal insulins reduced HbA\textsubscript{1c} levels from baseline to week 26 or 52 to a similar degree (by about 0.4% points [4 mmol/mol]), as would be expected with a treat-to-target trial design. In addition, non-inferiority was confirmed in both the intention-to-treat analyses and the per-protocol analyses.

Other measures of glycaemic control (fasting plasma glucose and self-measured fasting plasma glucose) showed little difference between insulin degludec and insulin glargine. In Heller et al. (2012), the mean self-measured fasting plasma glucose level before breakfast was statistically significantly lower with insulin degludec (once daily with the main evening meal) than with insulin glargine (once daily at the same time each day) at 52 weeks (estimated treatment difference −0.55 mmol/l, \(p=0.023\)). However, the clinical significance of this difference is unclear, especially because there was no statistically significant difference in fasting plasma glucose levels between the groups at this time point. In Mathieu et al. (2013), reductions in fasting plasma glucose levels were similar with once-daily insulin degludec dosed flexibly and insulin glargine at week 26, but greater with insulin degludec given once daily in the evening (estimated treatment difference between insulin degludec once daily dosed flexibly and insulin degludec once daily in the evening 0.95 mmol/l, \(p=0.021\)).

BEGIN Basal-Bolus Type 1 (Heller et al. 2012) also assessed health-related quality of life using the SF-36 health survey version 2. However, there were no statistically significant differences between insulin degludec (once daily with the main evening meal) and insulin glargine (once daily at the same time each day) in any of the domains of health-related quality of life, such as physical functioning, general health or mental health.

Both BEGIN Basal-Bolus Type 1 and BEGIN Flex T1 had extension phases (Bode et al. 2013 and Mathieu et al. 2013 respectively). In Bode et al. (2013), a similar proportion of participants in both groups entered the 52-week extension phase (74% [351/472] with insulin degludec; 75% [118/157] with insulin glargine). After 104 weeks, there was no statistically significant difference between the groups in glycaemic control (as would be expected with a treat-to-target trial design). The mean change in HbA\textsubscript{1c} levels from baseline to week 104 was −0.27% points with insulin degludec and −0.24% points with insulin glargine (estimated treatment difference −0.04% points; 95% confidence interval [CI] −0.17 to 0.09).
In Mathieu et al. (2013), 73% (239/329) of participants who were initially randomised to either insulin degludec once daily dosed flexibly or insulin degludec once daily in the evening entered a 26-week extension phase. In this extension phase, they were given insulin degludec dosed flexibly at any time of day (provided they maintained a minimum of 8 hours and a maximum of 40 hours between doses). In the insulin glargine arm, 81% (133/164) entered the extension phase, during which they continued to take insulin glargine at the same time each day. After 52 weeks, mean HbA₁c levels were higher than at 26 weeks in both groups, although they remained below baseline and were not statistically significantly different between groups. The mean change in HbA₁c from baseline to week 52 was −0.13% points (standard deviation 0.67) with insulin degludec, and −0.21% points (standard deviation 0.73) with insulin glargine (estimated treatment difference 0.07% points; 95% CI −0.05 to 0.19).

**Safety**

In both RCTs (Heller et al. 2012 and Mathieu et al. 2013), the proportion of participants reporting serious adverse events was similar with insulin degludec and insulin glargine (see tables 1 and 2). However, more participants withdrew because of adverse events in the insulin degludec groups in Mathieu et al. (2013) (3.0% with once-daily insulin degludec dosed flexibly, 2.4% with insulin degludec given once daily in the evening, and 0.6% with insulin glargine; statistical significance not reported). Injection-site reactions were numerically higher with once-daily insulin degludec dosed flexibly (4.9%) compared with insulin degludec given once daily in the evening (1.8%) or insulin glargine (2.5%), but again, statistical significance was not reported.

In BEGIN Basal-Bolus Type 1 (Heller et al. 2012), there was no statistically significant difference between insulin degludec and insulin glargine in the rates of confirmed episodes of overall hypoglycaemia, hypoglycaemia occurring during the day, or severe hypoglycaemia at week 52. The rate of nocturnal hypoglycaemia was statistically significantly lower with insulin degludec compared with insulin glargine. The rates of hypoglycaemia were as follows:

- 96% of participants reported confirmed overall hypoglycaemia in the insulin degludec group compared with 95% in the insulin glargine group (p=0.48)
- 94% of participants in both groups reported confirmed hypoglycaemia occurring during the day (p=0.30)
- 12% of participants reported severe hypoglycaemia in the insulin degludec group compared with 10% in the insulin glargine group (p=0.34)
- 72% of participants reported nocturnal confirmed hypoglycaemia in the insulin degludec group compared with 74% in the insulin glargine group (a reduction of about 1.5 episodes per patient per year of exposure, p=0.021).

The findings were similar at 104 weeks after the 52-week extension (Bode et al. 2013). There was no statistically significant difference between insulin degludec and insulin glargine in the rate of overall confirmed hypoglycaemia or severe hypoglycaemia, but there was a lower rate of nocturnal confirmed hypoglycaemia with insulin degludec (a reduction of about 1.4 episodes per patient per year of exposure, p=0.02).

In BEGIN Flex T1 (Mathieu et al. 2013), there was no statistically significant difference between insulin degludec once-daily dosed flexibly and insulin glargine in the rates of confirmed episodes of overall hypoglycaemia or severe hypoglycaemia at week 26. The rate of nocturnal confirmed hypoglycaemia was statistically significantly lower with insulin degludec once-daily dosed flexibly compared with insulin glargine. The rates of hypoglycaemia were as follows:

- 94% of participants reported overall confirmed hypoglycaemia in the insulin degludec once-daily dosed flexibly group compared with 97% in the insulin glargine group (not statistically significant)
- 10% of participants in both groups reported severe hypoglycaemia (not statistically significant)
- 68% of participants reported nocturnal confirmed hypoglycaemia in the insulin degludec once-daily dosed flexibly group compared with 73% in the insulin glargine group (a reduction of about 4 episodes per patient per year of exposure, p=0.001).

Once-daily insulin degludec dosed flexibly was also compared with insulin degludec given once daily in the evening in the BEGIN Flex T1 trial. There was no statistically significant difference between these groups in the rates of confirmed episodes of overall hypoglycaemia or severe hypoglycaemia at week 26. However, the rate of nocturnal confirmed hypoglycaemia was statistically significantly lower with insulin degludec once-daily dosed flexibly compared with insulin degludec given once daily in the evening. Nocturnal confirmed hypoglycaemia was reported by 68% of participants in the once-daily insulin degludec dosed flexibly group compared with 73% in the insulin degludec once daily in the evening group (a reduction of about 3.4 episodes per patient per year of exposure, p=0.003).

The findings were similar at 52 weeks after the 26-week extension. The rates of confirmed episodes of overall hypoglycaemia or severe hypoglycaemia were similar with once-daily insulin degludec dosed flexibly and once-daily insulin glargine, and the rate of nocturnal confirmed hypoglycaemia was statistically significantly lower with insulin degludec. Nocturnal confirmed hypoglycaemia was...
hypoglycaemia was reported by 77.8% of participants in the insulin degludec group compared with 78.3% in the insulin glargine group (a reduction of about 2 episodes per patient per year of exposure, p=0.026).

**Medicines and Healthcare Products Regulatory Agency (MHRA) advice**

Insulin degludec is the first insulin approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. The MHRA has issued the following advice to minimise the risk of medication errors associated with a 200 units/ml formulation (Drug Safety Update April 2013).

<table>
<thead>
<tr>
<th>Prescribing:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• When prescribing insulin degludec, ensure that the strength is included on the prescription.</td>
</tr>
<tr>
<td>• Do not convert (recalculate) doses when transferring patients from one strength of insulin degludec to another – the pen device shows the number of units of insulin to be injected irrespective of strength.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dispensing:</th>
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<tbody>
<tr>
<td>• Pharmacists should ensure that the correct strength of insulin degludec is dispensed; if in doubt, contact the prescriber.</td>
</tr>
<tr>
<td>• Pharmacists should ask patients to visually identify the strength of insulin degludec dispensed, and should ensure patients are able to read the dose counter of the pen device. Ask patients with poor vision to always seek assistance from a person who has good vision and is appropriately trained in use of the device.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients and healthcare staff must never use a syringe to withdraw insulin from a prefilled pen or from a cartridge.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfer from other medicines:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.</td>
</tr>
<tr>
<td>• For most patients, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous basal insulin dose with subsequent individual dose adjustments.</td>
</tr>
</tbody>
</table>
**Information to give to patients:**

- Patients should be aware that there are two different strengths of insulin degludec, and should be informed that the pen device will calculate the dose of insulin that they need irrespective of strength, so they simply need to check the dose-counter window of the pen device which displays the dose in units, and make sure this matches the dose they wish to administer. Patients must never count audible clicks to determine the dose of Tresiba to be administered.

- Patients should be provided with a patient booklet and Insulin Passport (or safety card), and should be trained on the correct use of Tresiba before the product is prescribed or dispensed.

- Warn patients that they should only use Tresiba as they have been trained because using it any other way may result in a dangerous overdose.

- Patients must be instructed to always check the manufacturer's packaging and dispensing label before every injection to ensure they have the correct insulin.

**Clinical management and storage:**

- Healthcare providers should risk assess electronic and paper systems used to prescribe, dispense and administer Tresiba. Carefully check the product strength selected in electronic systems.

- Risk assess the clinical storage arrangements for Tresiba to help ensure selection of the correct strength.

**Additional safety information**

The European Medicines Agency's (EMA's) European public assessment report on Tresiba provides further safety information on insulin degludec. It concluded that: 'Overall, the results of the clinical studies demonstrate that the use of insulin degludec in patients with type 1 and type 2 diabetes as monotherapy or in combination with oral antidiabetic agents is safe and in line with the safety profile of other insulin analogues.'

Several 'adverse events of special interest' were considered in the assessment report. These included:

- **Injection site reactions** which were reported at a similar rate with both strengths of insulin degludec and comparators. None of the injection site reactions was serious.
Neoplastic events which were reported as low and balanced between insulin degludec and comparator groups.

Cardiovascular safety which was assessed based on a meta-analysis of independently confirmed and blindly adjudicated major adverse cardiovascular events. The assessment report concluded that ‘the current data does not reveal an increased cardiovascular risk for insulin degludec treated patients’, and no pharmacovigilance activities are proposed. However, the US Food and Drug Administration has requested additional cardiovascular data from a dedicated cardiovascular outcomes trial before the review of the new drug application for insulin degludec can be completed in the USA.

Evidence strengths and limitations

The study design and analysis of results was appropriate in both studies (Heller et al. 2012 and Mathieu et al. 2013) to demonstrate non-inferiority of insulin degludec to insulin glargine in terms of glycaemic control. The primary end point in the RCTs was the surrogate outcome of change in HbA1c levels. As expected, there are no data on the effect of insulin degludec on patient-oriented, long-term complications of type 1 diabetes (such as microvascular or cardiovascular events) from RCTs designed to assess these clinical outcomes. Studies conducted over many years will be needed to generate such data; for example, such data only became available in 2012 for insulin glargine in type 2 diabetes, many years after it came to market (The ORIGIN Trial Investigators 2012).

The NICE clinical guideline on the diagnosis and management of type 1 diabetes recommends that basal insulin supply should be provided by the use of NPH (isophane) insulin or a long-acting insulin analogue. Although other long-acting insulin analogues, such as insulin glargine and insulin detemir, have been compared with NPH (isophane) insulin, there are no published studies comparing insulin degludec with NPH (isophane) insulin.

Like many studies of insulins, the RCTs had an open-label design because the different delivery devices of insulin degludec and insulin glargine prevented blinding. This could have affected how clinicians and patients used and viewed the different treatments. In turn, this could have affected the outcomes of the study, particularly subjective outcomes, such as symptomatic hypoglycaemia and quality of life (Tahrani et al. 2012). In addition, it is important to note that when patients did not complete the study, the method of last observation carried forward was used to fill in the missing data. In this approach, regardless of when a patient left the trial (for example, after week 1, week 6 or week 23), the last available result for that patient was carried forward and analysed as though it were the result at the study end.
As the EMA notes in its guideline on missing data in confirmatory clinical trials, it is unrealistic to expect that all participants in any clinical trial will receive treatment with full compliance to the treatment schedule and with a complete follow-up as per protocol. Some participants will drop out of the trial before the scheduled conclusion, and among those who stay in, some will have data not recorded for some reason. The guideline states that it is unacceptable simply to ignore such missing data, but there is no universally applicable method that adjusts the analysis to take these missing values into account, and different approaches may lead to different conclusions.

In the clinical trials discussed in this evidence summary, drop-out rates ranged from 14% to 16% among participants randomised to insulin degludec, and 7% to 13% among those randomised to insulin glargine. The EMA's guideline on missing data in confirmatory clinical trials notes that people who do not complete a clinical trial may be more likely to have extreme values than those who do (for example, treatment failure might lead to drop-out, whereas extremely good response might lead to loss of follow-up). Therefore, the loss of these 'non-completers' could lead to an underestimate of variability and hence artificially narrow the confidence interval for the treatment effect. In a superiority trial, this could lead to a false conclusion of a statistically significant result. Similarly, in a non-inferiority trial, this could lead to a false conclusion of non-inferiority. Only under certain restrictive assumptions does the method of last observation carried forward produce an unbiased estimate of the treatment effect. Moreover, it is not always the case that a last observation carried forward approach would tend to produce conservative estimates (that is, estimates unlikely to be biased in favour of the experimental treatment). Because the choice of primary analysis will be based on assumptions that cannot be verified, the EMA advises that it will almost always be necessary to investigate the robustness of trial results through appropriate sensitivity analyses that make different assumptions.

The safety end point of nocturnal confirmed hypoglycaemia was statistically significantly reduced with insulin degludec compared with insulin glargine. However, this difference was small in absolute terms. In the BEGIN Basal-Bolus Type 1 trial, there was a reduction of about 1.5 episodes of nocturnal hypoglycaemia per patient per year of treatment at 52 weeks (Heller et al. 2012) and about 1.4 episodes per patient per year at 104 weeks (Bode et al. 2013). There was no statistically significant reduction in overall, daytime or severe hypoglycaemia reported at 52 or 104 weeks. Similarly, in the BEGIN Flex T1 trial (Mathieu et al. 2013), there was a reduction of about 4 episodes of nocturnal hypoglycaemia per patient per year of treatment at 26 weeks and about 2 episodes per patient per year at 52 weeks. There was no statistically significant reduction in overall or severe hypoglycaemia at 26 or 52 weeks.
As highlighted earlier, there are no data showing how basal insulin degludec compares with basal NPH (isophane) insulin in terms of hypoglycaemic events, which would help local decision makers to be able to determine its place in therapy.

**Context**

**Treatment alternatives**

Basal insulin supply for adults with type 1 diabetes can be provided by:

- NPH (isophane) insulin (for example, Insulatard, Humulin I or Insuman Basal) or

- long-acting insulin analogues: insulin glargine (Lantus), insulin detemir (Levemir) or insulin degludec (Tresiba).

**Costs of treatment alternatives**

<table>
<thead>
<tr>
<th></th>
<th>5×3 ml cartridge (100 units/ml solution)</th>
<th>5×3 ml pre-filled pen (100 units/ml solution)</th>
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</thead>
<tbody>
<tr>
<td>Insulatard</td>
<td>£22.90</td>
<td>£20.40</td>
</tr>
<tr>
<td>Humulin I</td>
<td>£19.08</td>
<td>£21.70</td>
</tr>
<tr>
<td>Insuman Basal</td>
<td>£17.50</td>
<td>£19.80</td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>£41.50</td>
<td>£41.50</td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>£42.00</td>
<td>£42.00</td>
</tr>
<tr>
<td>Insulin degludec (Tresiba)</td>
<td>£72.00</td>
<td>£72.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(£86.40 for 3×3 ml 200 units/ml solution)</td>
</tr>
</tbody>
</table>

Costs are excluding VAT; taken from MIMS (July 2013).
Estimated impact for the NHS

Likely place in therapy

The NICE clinical guideline on type 1 diabetes (which is currently being updated; publication date to be confirmed) recommends that basal insulin supply for adults should be provided by NPH (isophane) insulin or a long-acting insulin analogue. The guideline refers specifically to the long-acting insulin analogue, insulin glargine. It does not mention insulin detemir or insulin degludec because these were not available when the guideline was produced. These insulins will be included in the update of the NICE clinical guideline on type 1 diabetes.

Regarding the choice of insulin therapy, there is little difference between the long-acting insulin analogues that have been available for some time (insulin glargine and insulin detemir) and NPH (isophane) insulin for lowering HbA1c levels in type 1 diabetes. Compared with NPH (isophane) insulin, both these long-acting insulin analogues have been associated with statistically significantly lower rates of some, but not all, measures of hypoglycaemia in people with type 1 diabetes (CADTH Technology Overview 2010). The NICE clinical guideline on type 1 diabetes recommends that a long-acting insulin analogue should be used when:

- nocturnal hypoglycaemia is a problem on NPH (isophane) insulin
- morning hyperglycaemia on NPH (isophane) insulin results in difficult daytime blood glucose control
- rapid-acting insulin analogues are used for mealtime blood glucose control.

Based on the results of the studies by Heller et al. (2012) and Mathieu et al. (2013), insulin degludec is likely to be marketed as a basal insulin for type 1 diabetes with potential benefits in reducing nocturnal hypoglycaemia (Ratner et al. 2013). However, the limitations of the study (discussed in the section on evidence strengths and limitations) need to be considered. The absolute difference in nocturnal hypoglycaemic rates from insulin glargine was statistically significant but small in absolute terms (between 1.4 and 4 episodes per patient per year). There is also no comparison with NPH (isophane) insulin, no patient oriented efficacy outcome data and no information on the efficacy or safety of insulin degludec over longer than the two year data currently available.

The concerns over a possible risk of medication errors with the double-strength 200 units/ml formulation also need to be considered. The Medicines and Healthcare Products Regulatory Agency has issued advice to minimise the risk of medication errors associated with this higher
strength formulation, a 200 units/ml prefilled pen device (see the section on safety for more information; Drug Safety Update April 2013).

The Health and Social Care Information Centre report, Prescribing for diabetes in England - 2005-2006 to 2011-2012, stated that the net ingredient cost of insulin therapy in primary care in 2011/12 was £314.7 million: a growth of 42.5% from 2005/6 to 2011/12. In the year to September 2012, 1.3 million items of insulin glargine were prescribed at a cost of nearly £78 million, and just over 650,000 items of insulin detemir at a cost of £41 million. This compared with 370,000 items of NPH (isophane) insulin at a cost of just over £13 million (NHS Business Services Authority: personal communication July 2013).

The cost of insulin degludec 100 units/ml is £72.00 for 5×3 ml cartridges or pre-filled pens. This is more expensive than similar formulations of insulin glargine and insulin detemir, which are £41.50 and £42.00 respectively. NPH (isophane) insulin formulations are about half the cost of insulin glargine or detemir, at between £17.50 and £22.90.

**Estimated usage**

The manufacturer has estimated an uptake of 5%, 10% and 15% of the eligible population in years 1, 2 and 3 respectively. It has defined the eligible population as adults (18 years or over) with type 1 diabetes currently on a basal long-acting insulin analogue (not basal NPH [isophane] insulin). Based on these estimates, for a population of 100,000 patients, this translates to the use of insulin degludec in 11 patients in year 1, 22 patients in year 2 and 33 patients in year 3 (Novo Nordisk: personal communication August 2012).

Estimated usage in type 2 diabetes is given in the evidence summary on insulin degludec in type 2 diabetes.

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Medicines and Healthcare Products Regulatory Agency (April 2013) Insulin degludec (Tresiba▼): available in additional higher strength than existing insulins—care needed to minimise risk of error, including training for patients. Drug Safety Update 6 (issue 9): A1


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About this evidence summary

‘Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – integrated process statement.

Changes after publication

October 2015: Minor maintenance

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ISBN: 978-1-4731-0292-7