NICE advice

Type 2 diabetes: insulin degludec

Evidence summary
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nice.org.uk/guidance/esnm25

This advice replaces ESNM4.

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 2 diabetes, with statistically significantly lower rates of some, but not all, measures of hypoglycaemia, particularly nocturnal hypoglycaemia. Although there are published studies with one year data, there are none comparing insulin degludec with NPH (isophane) insulin and none that measure patient-oriented efficacy outcomes.

Effectiveness	Safety
• Insulin degludec is non-inferior to insulin glargine for glycaemic control – Insulin degludec reduced HbA_{1c} by about 1.1% points [12 mmol/mol] from baseline (2 RCTs, 52 weeks). • Insulin degludec statistically significantly improved glycaemic control compared with sitagliptin – estimated treatment difference in HbA_{1c} 0.43% points [5 mmol/mol] (1 RCT, 26 weeks).	• 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	Resource implications
• Once daily, with flexibility in timing of administration. SmPC states that a minimum of 8 hours between injections should always be ensured. • Compared with insulin glargine: – similar tolerability – statistically significant reductions in hypoglycaemic events (various definitions of between 0.02 and 2.5 episodes per patient per year) (2 RCTs, 52 weeks). • Compared with sitagliptin: – more withdrawals because of adverse effects: 3.9% compared with 0.9% (1 RCT, 26 weeks) – statistically significant increase in overall hypoglycaemia of 1.81 episodes per patient per year (1 RCT, 26 weeks).	• 5×3 ml cartridges (100 units/ml) and 5×3 ml pre-filled pen (100 units/ml), £72.00. • 3×3 ml pre-filled pen (200 units/ml), £86.40. • More expensive than NPH (isophane) insulin, insulin glargine and insulin detemir.

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 2 diabetes. It supersedes an earlier evidence summary (ESNM4), published in November 2012. Another evidence summary considers its use in adults with type 1 diabetes.

This evidence summary is based on the 3 randomised controlled trials (RCTs) that provide the best (highest quality) available published evidence relating to the efficacy and safety of insulin degludec to treat people with type 2 diabetes. In these trials, insulin degludec was compared with insulin glargine in people who had previously used basal insulin (Garber et al. 2012) and in people who

were insulin naive (Zinman et al. 2012). Insulin degludec was also compared with sitagliptin in people who were insulin naive (Philis-Tsimikas et al. 2013). Two other published phase III studies (Meneghini et al. 2013 and Gough et al. 2013) are discussed briefly in the evidence review section.

Evidence from the 2 open-label RCTs comparing insulin degludec with insulin glargine indicates that insulin degludec is non-inferior to insulin glargine in terms of glycaemic control: both basal insulins reduced glycated haemoglobin (HbA_{1c}) 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 overall hypoglycaemia, nocturnal hypoglycaemia and (in a post-hoc analysis) daytime hypoglycaemia, compared with insulin glargine in 1 RCT (Garber et al. 2012); and nocturnal hypoglycaemia and severe hypoglycaemia in the other RCT (Zinman et al. 2012). However, the absolute differences in these rates were small and the findings relating to severe hypoglycaemia, in particular, need to be viewed with caution because of very low event rates. Although these studies include data at one year, there are no published studies comparing insulin degludec with NPH (isophane) insulin and none that measure patient-oriented efficacy outcomes.

Compared with sitagliptin, insulin degludec was superior in terms of glycaemic control, but resulted in more episodes of overall confirmed hypoglycaemia (Philis-Tsimikas et al. 2013). However, because insulin was titrated weekly in a treat-to-target approach, and the mean insulin dose increased throughout the trial, these results may be expected.

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 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87; which is currently being updated) recommends that, when insulin therapy is necessary, human NPH (isophane) insulin is the preferred option. Examples of NPH (isophane) insulin include Insulatard, Humulin I or Insuman Basal. The guideline recommends that the long-acting insulin analogues, insulin glargine and insulin detemir, can be considered as an alternative in some people, for example those who

need assistance from a carer or healthcare professional to inject their insulin, or whose lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes. 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 2 diabetes alongside that for other basal insulins, taking into account the current NICE guidance which recommends the use of long-acting insulin analogues in some limited circumstances. 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

Garber AJ, King AB, Del Prato S et al. (2012) Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. The Lancet 379: 1498–507 doi: 10.1016/S0140-6736(12)60205-0

Zinman B, Philis-Tsimikas A, Cariou B et al. (2012) Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 35: 2464–71 doi: 10.2337/dc12-1205

Philis-Tsimikas A, Del Prato S, Satman I et al. (2013) Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. Diabetes, Obesity and Metabolism 15: 760–6 doi: 10.1111/dom.12115

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.

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 in type 2 diabetes will be included in the update of the NICE clinical guideline on the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

Introduction

The NICE clinical guideline on the management of type 2 diabetes states that the management of type 2 diabetes is complex. It requires an individualised, multifactorial approach that addresses blood pressure, blood lipids, and lifestyle issues (for example, smoking cessation, exercise, losing weight and a healthy diet). Controlling blood glucose requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The NICE clinical guideline recommends that patients should be involved in setting their individualised HbA_{1c} target level, which may be above the general target of 48 mmol/mol (6.5%). The guideline also recommends that pursuing highly intensive management to HbA_{1c} levels below 48 mmol/mol (6.5%) should be avoided.

Clinical trial evidence suggests there are small absolute benefits for intensive blood glucose control compared with conventional control in people with type 2 diabetes on some macrovascular outcomes. Intensive control has been shown to reduce coronary heart disease, but the evidence is less clear for the benefits on stroke, death from cardiovascular disease or death from all causes. This needs to be balanced against the increased risk of severe hypoglycaemia with intensive blood glucose control. Studies have also shown a reduction in certain microvascular events with intensive blood glucose control. However, these results have been inconsistent, and some end points were disease-oriented surrogate outcomes rather than patient-oriented clinical outcomes. See the MeReC Bulletin on type 2 diabetes (March 2012), the type 2 diabetes key therapeutic topic and the NICE pathway on diabetes for more information. See also the Clinical Knowledge Summary on type 2 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 2 diabetes. (A combination preparation containing both insulin degludec and insulin aspart has also been licensed but has not yet been marketed within 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 people with type 2 diabetes mellitus, it can be administered alone, in combination with oral antidiabetic drugs as well as in combination with bolus insulin. 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 3×3 ml – 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 2 diabetes that have been published in full:

- BEGIN Basal-Bolus Type 2 of insulin degludec compared with insulin glargine in people who had previously used basal insulin (Garber et al. 2012; see table 1). This study was originally reviewed in ESNM4 Type 2 diabetes: insulin degludec, which this ESNM has superseded.
- BEGIN Once Long of insulin degludec compared with insulin glargine in people who were insulin naive (Zinman et al. 2012; see table 2).
- BEGIN Early of insulin degludec compared with sitagliptin in people who were insulin naive (Philis-Tsimikas et al. 2013; see table 3).

Two other phase III studies that have been published in full, BEGIN Flex (Meneghini et al. 2013) and BEGIN Low Volume (Gough et al. 2013), are discussed briefly for context in the clinical effectiveness section.

BEGIN Basal-Bolus Type 2 (Garber et al. 2012)

- Design: open-label, non-inferiority, 52-week randomised controlled trial (RCT). Allocation concealed.
- Population: 1006 adults (mean age just under 60 years across 123 sites in 12 countries) with type 2 diabetes (BMI 40 kg/m^2 or less) and HbA_{1c} 53–86 mmol/mol (7.0–10.0%) after using any insulin regimen (with or without oral antidiabetic drugs) for 3 months or longer. All oral antidiabetic drugs were stopped at randomisation apart from metformin or pioglitazone. About 60% continued metformin alone or in combination and 7% or less continued pioglitazone alone or in combination. Mean HbA_{1c} was around 67 mmol/mol (8.3%) and mean BMI was around 32 kg/m^2.
- Intervention and comparison: subcutaneous insulin degludec (100 units/ml) once daily in the evening compared with subcutaneous insulin glargine (100 units/ml, once daily, at the same

time each day), both in combination with subcutaneous mealtime 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. It was recommended that bolus insulin was titrated after the basal insulin had been titrated.

- 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 2: Garber et al. (2012)

	Insulin degludec	Insulin glargine	Analysis
Randomised	n=755	n=251	
Efficacy Full analysis set[a] (ITT group)	n=744	n=248	
Primary outcome: mean change in HbA_{1c} from baseline to week 52	−1.10% points from baseline of 8.3% (67 mmol/mol)	−1.18% points from baseline of 8.4% (68 mmol/mol)	Estimated treatment difference in the ITT group 0.08% points (95% CI −0.05 to 0.21; for 1-sided test of non-inferiority[b] evaluated at the 2.5% level) Estimated treatment difference in the per-protocol[c] analysis 0.05% points (95% CI −0.08 to 0.18)
Selected secondary outcomes:			
Mean change in FPG from baseline to week 52	−2.3 mmol/l	−2.0 mmol/l	Estimated treatment difference −0.29 mmol/l (95% CI −0.65 to 0.06; p=0.1075)
Safety Safety analysis set[d]	n=753	n=251	

Participants with severe hypoglycaemia (needing assistance)	5% (34/753) 0.06 per PYE	4% (11/251) 0.05 per PYE	Insufficient episodes for statistical assessment of estimated rate ratio
Participants with overall confirmed[e] hypoglycaemia	81% (609/753) 11.09 per PYE	82% (206/251) 13.63 per PYE	Estimated rate ratio 0.82 (95% CI 0.69 to 0.99; p=0.0359)
Participants with nocturnal confirmed[e] hypoglycaemia	40% (298/753) 1.39 per PYE	47% (119/251) 1.84 per PYE	Estimated rate ratio 0.75 (95% CI 0.58 to 0.99; p=0.0399)
Participants with diurnal confirmed[e] hypoglycaemia	78% (586/753) 9.28 per PYE	79% (198/251) 11.39 per PYE	Estimated rate ratio 0.82 (95% CI 0.684 to 0.995; p=0.044) based on post-hoc analysis[f]
Participants reporting serious adverse events	15% (112/753) 21 events per 100 PYE	16% (40/251) 20 events per 100 PYE	There was no statistically significant difference
Mean weight gain	3.6 kg (SD 4.9)	4.0 kg (SD 4.6)	Statistical significance not reported
Injection-site reactions	4% (27/753)	3% (7/251)	Statistical significance not reported

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, excluding 14 patients from 1 closed trial site.

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

[c] All participants who had at least 12 weeks' exposure to treatment, who did not have any major protocol violations, and who had valid assessments of HbA_{1c} at baseline and at or after 12 weeks of treatment (insulin degludec, n=694; insulin glargine, n=233).

[d] All participants who received at least 1 dose of study drug.

[e] Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3.1 mmol/l (irrespective of symptoms) or severe episodes needing assistance.

BEGIN Once Long (Zinman et al. 2012)

- Design: open-label, non-inferiority, 52-week RCT with a 52-week extension (not yet fully published). Allocation concealed.
- Population: 1030 insulin-naive adults (mean age 59 years across 166 sites in 12 countries) with type 2 diabetes (BMI 40 kg/m^2 or less) and HbA_{1c} 53–86 mmol/mol (7.0–10.0%) after taking oral antidiabetic drugs (metformin monotherapy or metformin in any combination with a sulfonylurea, a glinide, a gliptin or acarbose for 3 months or longer). Participants were excluded if they received a glitazone, exenatide or liraglutide within 3 months of screening. At randomisation, participants discontinued all oral antidiabetic drugs apart from metformin and a gliptin. Mean HbA_{1c} was 66 mmol/mol (8.2%) and mean BMI was around 31 kg/m^2.
- Intervention and comparison: subcutaneous insulin degludec (100 units/ml) once daily with the main evening meal compared with subcutaneous insulin glargine (100 units/ml, once daily, at the same time each day), in a treat-to-target approach. Basal insulin was titrated to aim for self-measured plasma glucose concentrations of between 3.9 mmol/l and 4.9 mmol/l before breakfast.
- 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 and frequency of 'responders' for HbA_{1c} less than 7.0% (53 mmol/mol).

Table 2 Summary of BEGIN Once Long: Zinman et al. (2012)

	Insulin degludec	Insulin glargine	Analysis
Randomised	n=773	n=257	
Efficacy Full analysis set[a] (ITT group)	n=773	n=257	
Primary outcome: mean change in HbA_{1c} from baseline to week 52	−1.06% points from a baseline of 8.2% (66 mmol/mol)	−1.19% points from a baseline of 8.2% (66 mmol/mol)	Estimated treatment difference in the ITT group 0.09% points (95% CI −0.04 to 0.22) confirms non-inferiority[b] Estimated treatment difference in the per-protocol[c] analysis 0.13% points (95% CI −0.01 to 0.26)
Selected secondary outcomes:			
Mean change in FPG from baseline to week 52	−3.8 mmol/l	−3.3 mmol/l	Estimated treatment difference −0.43 mmol/l (95% CI −0.74 to 0.13; p=0.005)
Participants achieving HbA_{1c} concentrations <7.0% (53 mmol/mol) at week 52	52% (400/773)	54% (139/257)	p=0.40 No statistically significant difference
Safety (safety analysis set[d])	n=766	n=257	
Participants with severe hypoglycaemia (needing assistance)	0.3% (2/766) 0.003 per PYE	1.9% (5/257) 0.023 per PYE	Estimated rate ratio 0.14 (95% CI 0.03 to 0.70; p=0.017)
Participants with overall confirmed[e] hypoglycaemia	46.5% (356/766) 1.52 per PYE	46.3% (119/257) 1.85 per PYE	Estimated rate ratio 0.82 (95% CI 0.64 to 1.04; p=0.106) No statistically significant difference

Participants with nocturnal confirmed[e] hypoglycaemia	13.8% (106/766) 0.25 per PYE	15.2% (39/257) 0.39 per PYE	Estimated rate ratio 0.64 (95% CI 0.42 to 0.98; p=0.038)
Participants reporting serious adverse events	8.1% (62/766)	10.1% (26/257)	Statistical significance not reported
Mean weight gain	2.4 kg	2.1 kg	p=0.28 No statistically significant difference
Injection-site reactions	0.10 per PYE	0.13 per PYE	Statistical significance not reported

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

[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 less than or equal to 0.4% points (4.4 mmol/mol), as recommended by regulatory guidelines.

[c] All participants who had at least 12 weeks' exposure to treatment, who did not have any major protocol violations, and who had valid assessments of HbA_{1c} at baseline and at or after 12 weeks of treatment (insulin degludec, n=665; insulin glargine, n=221).

[d] All participants 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 (irrespective of symptoms) or severe episodes needing assistance.

BEGIN Early (Philis-Tsimikas et al. 2013)

- Design: open-label, superiority, 26-week RCT. Allocation concealed.
- Population: 458 insulin-naive adults (mean age 56 years across 78 sites in 7 countries) with type 2 diabetes (BMI 40 kg/m^2 or less) and HbA_{1c} 58–98 mmol/mol (7.5–11.0%) after using 1 or 2 oral antidiabetic drugs, including metformin, sulfonylureas, glinides or pioglitazone in any combination, with an unchanged dose, for at least 3 months. Mean HbA_{1c} was around 74 mmol/mol (8.9%) and mean BMI was around 30 kg/m^2.
- Intervention and comparison: subcutaneous insulin degludec (100 units/ml) once daily at any time of day (minimum of 8 hours and maximum of 40 hours between injections) compared with

sitagliptin 100 mg tablet (once daily), as add-on to stable treatment with 1 or 2 oral antidiabetic drugs. Insulin degludec was given in a treat-to-target approach, aiming for self-measured plasma glucose concentrations of less than 5.0 mmol/l before breakfast.

- Outcome: the primary outcome was change from baseline in HbA_{1c} after 26 weeks of treatment, in the intention-to-treat population. Secondary outcomes included change from baseline in fasting plasma glucose and frequency of 'responders' for HbA_{1c} less than 7.0% (53 mmol/mol) at the end of the trial, and at the end of the trial without confirmed hypoglycaemic episodes.

Table 3 Summary of BEGIN Early: Philis-Tsimikas et al. (2013)

	Insulin degludec	Sitagliptin	Analysis
Randomised	n=229	n=229	
Efficacy Full analysis set[a] (ITT group)	n=225	n=222	
Primary outcome: mean change in HbA_{1c} from baseline to week 26	−1.52% points from baseline of 8.8% (73 mmol/mol)	−1.09% points from baseline of 9.0% (75 mmol/mol)	Estimated treatment difference −0.43% (95% CI −0.61 to −0.24; p<0.0001)
Selected secondary outcomes:			
Mean change in FPG from baseline to week 26	−3.41 mmol/l	−1.24 mmol/l	Estimated treatment difference −2.17 mmol/l (95% CI −2.59 to −1.74; p<0.0001)
Participants achieving HbA_{1c} concentrations <7.0% (53 mmol/mol) at week 26	41% (patient numbers not reported)	28% (patient numbers not reported)	Estimated OR 1.60 (95% CI 1.04 to 2.47; p=0.034)
Participants achieving HbA_{1c} concentrations <7.0% [53 mmol/mol] without hypoglycaemia at week 26	25% (patient numbers not reported)	23% (patient numbers not reported)	Estimated OR 0.92 (95% CI 0.55 to 1.53) No statistically significant difference

Safety (safety analysis set[b])	n=226	n=228	
Participants with severe hypoglycaemia (needing assistance)	0.4% (1/226) 0.01 per PYE	0% (0/228) 0.00 per PYE	Insufficient episodes for statistical assessment of estimated rate ratio
Participants with overall confirmed[c] hypoglycaemia	42.5% (96/226) 3.07 per PYE	12.7% (29/228) 1.26 per PYE	Estimated rate ratio 3.81 (95% CI 2.40 to 6.05; p<0.0001)
Participants with nocturnal confirmed[c] hypoglycaemia	12.8% (29/226) 0.52 per PYE	5.7% (13/228) 0.30 per PYE	Estimated rate ratio 1.93 (95% CI 0.90 to 4.10; p=0.09) No statistically significant difference
Participants reporting adverse events	62.4% (141/226)	63.2% (144/228)	No statistical testing reported
Participants reporting serious adverse events	6.2% (14/226) 17 events per 100 PYE	4.4% (10/228) 10 events per 100 PYE	No statistical testing reported
Participants reporting adverse events leading to discontinuation	3.9% (9/229)	0.9% (2/229)	No statistical testing reported
Mean weight change	+2.28 kg	−0.35 kg	Estimated treatment difference 2.75 kg (95% CI 1.97 to 3.54; p<0.0001)
Injection-site reactions	4.4% (10/226)	Not applicable	

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

[a] All participants who were randomly assigned to treatment, excluding patients from 1 closed trial site.

[b] All participants exposed to treatment.

[c] Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3.1 mmol/l (irrespective of symptoms) or severe episodes needing assistance.

Clinical effectiveness

Insulin degludec compared with insulin glargine

Two open-label RCTs compared insulin degludec with insulin glargine. One in people who had previously used basal insulin (Garber et al. 2012) and the other in people who were insulin naive (Zinman et al. 2012). Both RCTs found insulin degludec was non-inferior to insulin glargine in terms of glycaemic control. Both basal insulins reduced HbA_{1c} levels from baseline to week 52 to a similar degree (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.

In BEGIN Basal-Bolus Type 2 (Garber et al. 2012), the reduction in fasting plasma glucose was similar between the insulins. However, in BEGIN Once Long (Zinman et al. 2012), the reduction in fasting plasma glucose levels was statistically significantly greater with insulin degludec compared with insulin glargine (estimated treatment difference −0.43 mmol/l; 95% confidence interval [CI] −0.74 to 0.13, p=0.005).

Both RCTs reported effects on health-related quality of life using the SF-36 health survey version 2. In BEGIN Basal-Bolus Type 2 (Garber et al. 2012), there was a statistically significant difference of 1.4 points (95% CI 0.1 to 2.7, p=0.0320) for the domain of 'bodily pain' in favour of insulin degludec. In BEGIN Once Long (Zinman et al. 2012), there were statistically significant differences favouring insulin degludec for the domains of 'overall physical' (1.0 points; 95% CI 0.1 to 2.0, p=0.033) and 'physical functioning' (1.4 points; 95% CI 0.3 to 2.4, p=0.016). However, the clinical significance of these changes is unclear. There were no other statistically significant differences reported between insulin degludec and insulin glargine in other domains of health-related quality of life in these RCTs, such as general health or mental health.

Insulin degludec compared with sitagliptin

In BEGIN Early (Philis-Tsimikas et al. 2013), insulin degludec was superior to sitagliptin in terms of glycaemic control in people who were insulin naive. After 26 weeks of treatment, HbA_{1c} levels were reduced by 1.52% with insulin degludec compared with a reduction of 1.09% with sitagliptin (estimated treatment difference −0.43% (95% CI −0.61 to −0.24; p<0.0001). The reduction in fasting plasma glucose levels from baseline was also statistically significantly greater with insulin degludec compared with sitagliptin (estimated treatment difference −2.17 mmol/l; 95% CI −2.59 to −1.74; p<0.0001).

More participants achieved an HbA_{1c} level of less than 7.0% points (53 mmol/mol) at the end of the trial with insulin degludec compared with sitagliptin (41% compared with 28%, odds ratio [OR] 1.60; 95% CI 1.04 to 2.47; p=0.034). However, the proportion of participants achieving this HbA_{1c} target without experiencing confirmed hypoglycaemic episodes was not statistically significantly different (25% with insulin degludec and 23% with sitagliptin, OR 0.92; 95% CI 0.55 to 1.53).

This RCT reported effects on health-related quality of life using the SF-36 health survey version 2; effects appeared to be similar between insulin degludec and sitagliptin.

Insulin degludec flexible dosing

In BEGIN Early (Philis-Tsimikas et al. 2013), insulin degludec could be given once daily at any time of day, with a minimum of 8 hours and maximum of 40 hours between injections. During the trial, 42% of participants chose to change the time of their injection on at least 1 occasion.

The efficacy and safety of variable once-daily dosing intervals of insulin degludec (100 units/ml) has been evaluated in the open-label, treat-to-target RCT, BEGIN Flex (Meneghini et al. 2013). In this trial, once-daily insulin degludec in a prespecified flexible dosing schedule, creating 8 to 40 hour intervals between injections, was compared with once-daily insulin degludec (100 units/ml) at the main evening meal, or once-daily insulin glargine (100 units/ml) at the same time each day. Participants had type 2 diabetes and were either insulin naive and taking oral antidiabetic drugs, or previously on basal insulin with or without oral antidiabetic drugs. After 26 weeks, variable once-daily dosing of insulin degludec was non-inferior to insulin glargine for glycaemic control, with no statistically significant difference in overall or nocturnal hypoglycaemia (see table 4). Severe hypoglycaemia was rare (2 episodes in each treatment group).

Table 4 Key results from BEGIN Flex: Meneghini et al. (2013)

	Insulin degludec variable once-daily dosing (n=229)	Insulin degludec once daily (n=228)	Insulin glargine once daily (n=230)	Analysis
Primary outcome: mean change in HbA_{1c} from baseline to week 26	−1.28% points from a baseline of 8.5% (69 mmol/mol)	−1.07% points from a baseline of 8.4% (68 mmol/mol)	−1.26% points from a baseline of 8.4% (68 mmol/mol)	Estimated treatment difference between insulin degludec flexible dosing and insulin glargine 0.04% points (95% CI −0.12 to 0.20) confirms non-inferiority[a]
Participants with overall confirmed[b] hypoglycaemia	51% (117/230) 3.6 per PYE	44% (99/226) 3.6 per PYE	49% (113/229) 3.5 per PYE	Estimated rate ratio between insulin degludec flexible dosing and insulin glargine 1.03 (95% CI 0.75 to 1.40; not statistically significant)
Participants with nocturnal confirmed[b] hypoglycaemia	13% (31/230) 0.6 per PYE	11% (24/226) 0.6 per PYE	21% (49/229) 0.8 per PYE	Estimated rate ratio between insulin degludec flexible dosing and insulin glargine 0.77 (95% CI 0.44 to 1.35; not statistically significant)

Abbreviations: CI, confidence interval; n, number of patients; PYE, patient-years of exposure.

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

[b] Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3.1 mmol/l (irrespective of symptoms) or severe episodes needing assistance.

Insulin degludec: higher strength

Insulin degludec is available in the European Union-wide standard strength for insulin of 100 units/ml and also in a higher strength 200 units/ml formulation. 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).

The efficacy and safety of the 200 units/ml formulation has been evaluated in the open-label, treat-to-target RCT, BEGIN Low Volume (Gough et al. 2013). In this trial, subcutaneous once-daily insulin degludec 200 units/ml with the main evening meal was compared with subcutaneous once-daily insulin glargine 100 units/ml at the same time each day in people with type 2 diabetes who were insulin naive and taking oral antidiabetic drugs, but qualified for intensification of treatment. After 26 weeks, higher strength insulin degludec was non-inferior to insulin glargine for glycaemic control, with no statistically significant difference in overall or nocturnal hypoglycaemia (see table 5). There were no reports of severe hypoglycaemia in either group.

Table 5 Key results of BEGIN Low Volume: Gough et al. (2013)

	Insulin degludec 200 units/ml (n=228)	Insulin glargine 100 units/ml (n=229)	Analysis
Primary outcome: mean change in HbA_{1c} from baseline to week 26	1.3% points from a baseline of 8.3% (67 mmol/mol)	1.3% points from a baseline of 8.2% (67 mmol/mol)	Estimated treatment difference 0.04% points (95% CI −0.11 to 0.19) confirms non-inferiority[a]
Secondary outcome: mean change in FPG from baseline to week 26	−3.7 mmol/l	−3.4 mmol/l	Estimated treatment difference −0.42 mmol/l (95% CI −0.78 to −0.06)
Participants with overall confirmed[b] hypoglycaemia	28.5% (65/228) 1.22 per PYE	30.7% (70/228) 1.42 per PYE	Estimated rate ratio 0.86 (95% CI 0.58 to 1.28) No statistically significant difference
Participants with nocturnal confirmed[b] hypoglycaemia	6.1% (14/228) 0.18 per PYE	8.8% (20/228) 0.28 per PYE	Estimated rate ratio 0.64 (95% CI 0.30 to 1.37) No statistically significant difference

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; n, number of patients; PYE, patient-years of exposure.

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

[b] Confirmed hypoglycaemia was defined as those episodes in which the self-measured blood glucose value was lower than 3.1 mmol/l (irrespective of symptoms) or severe episodes needing assistance.

Safety

Insulin degludec compared with insulin glargine

In both RCTs (Garber et al. 2012 and Zinman et al. 2012), the proportion of participants reporting adverse events and the proportion who withdrew because of adverse events were similar with insulin degludec or insulin glargine. The rates of serious adverse events were also similar between the 2 groups in both trials (see tables 1 and 2).

With regard to hypoglycaemia, in BEGIN Basal-Bolus Type 2 (Garber et al. 2012), the rates of confirmed episodes of overall hypoglycaemia, nocturnal hypoglycaemia and (in a post-hoc analysis) hypoglycaemic episodes occurring during the day (diurnal hypoglycaemia) were statistically significantly lower with insulin degludec compared with insulin glargine at week 52. The rates of hypoglycaemia were as follows:

- 81% of participants reported confirmed overall hypoglycaemia in the insulin degludec group compared with 82% in the insulin glargine group (a reduction of about 2.5 episodes per patient per year of exposure, p=0.0359).
- 40% of participants reported confirmed nocturnal hypoglycaemia in the insulin degludec group compared with 47% in the insulin glargine group (a reduction of about 0.5 episodes per patient per year of exposure, p=0.0399).
- 78% of participants reported confirmed diurnal hypoglycaemia in the insulin degludec group compared with 79% in the insulin glargine group (a reduction of about 2.1 episodes per patient per year of exposure, p=0.044).

The rates of severe hypoglycaemia were similar between the 2 groups, and owing to low numbers of severe hypoglycaemic events, it was not possible to assess for statistically significant differences.

In BEGIN Once Long (Zinman et al. 2012), there was no statistically significant difference between insulin degludec and insulin glargine in confirmed episodes of overall hypoglycaemia at week 52. Confirmed episodes of nocturnal hypoglycaemia were statistically significantly lower with insulin degludec compared with insulin glargine, as were episodes of severe hypoglycaemia. However, very low numbers of severe hypoglycaemic episodes were reported in each group (2 out of 766 participants in the degludec group and 5 out of 257 participants in the glargine group), and this result should be viewed with caution. The rates of hypoglycaemia were as follows:

- 46.5% of participants reported confirmed overall hypoglycaemia in the insulin degludec group compared with 46.3% in the insulin glargine group (p=0.106).
- 13.8% of participants reported confirmed nocturnal hypoglycaemia in the insulin degludec group compared with 15.2% in the insulin glargine group (a reduction of about 0.14 episodes per patient per year of exposure, p=0.038).
- 0.3% of participants reported severe hypoglycaemia in the insulin degludec group compared with 1.9% in the insulin glargine group (a reduction of about 0.02 episodes per patient per year of exposure, p=0.017).

Insulin degludec compared with sitagliptin

In BEGIN Early (Philis-Tsimikas et al. 2013), the proportion of participants reporting adverse events and serious adverse events was similar with insulin degludec and sitagliptin. However, more participants withdrew because of adverse events with insulin degludec (3.9% in the insulin degludec group compared with 0.9% in the sitagliptin group; statistical significance not reported).

The rate of confirmed episodes of overall hypoglycaemia was statistically significantly higher with insulin degludec compared with sitagliptin (3.07 episodes per patient per year of exposure with insulin degludec compared with 1.26 episodes per patient per year of exposure with sitagliptin, difference 1.81, p<0.0001). For confirmed nocturnal hypoglycaemia, the increased rate with insulin degludec was not statistically significant (0.52 episodes per patient per year of exposure with insulin degludec compared with 0.30 episodes per patient per year of exposure with sitagliptin, p=0.09).

Insulin degludec increased body weight from baseline (+2.28 kg) compared with no increase with sitagliptin (−0.35 kg; p<0.0001).

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).

Prescribing:

- When prescribing insulin degludec, ensure that the strength is included on the prescription.
- 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.

Dispensing:

- Pharmacists should ensure that the correct strength of insulin degludec is dispensed; if in doubt, contact the prescriber.
- 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

Administration:

- Patients and healthcare staff must never use a syringe to withdraw insulin from a prefilled pen or from a cartridge.

Transfer from other medicines:

- 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.
- 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.

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 to demonstrate non-inferiority of insulin degludec to insulin glargine in terms of glycaemic control in people who had previously used basal insulin in BEGIN Basal-Bolus Type 2 (Garber et al. 2012) and in people who were insulin naive in BEGIN Once Long (Zinman et al. 2012).

The primary end point in these RCTs was the surrogate outcome of change in HbA_{1c} levels. As expected, there are no data on the effect of insulin degludec on patient-oriented, long-term complications of type 2 diabetes (such as cardiovascular or microvascular 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, many years after it came to market (The ORIGIN Trial Investigators 2012).

NPH (isophane) insulin is the preferred basal insulin recommended in the NICE clinical guideline on the management of type 2 diabetes. 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.

The publication of BEGIN Early (Philis-Tsimikas et al. 2013) is helpful in allowing us to compare the strategies of adding a basal insulin (insulin degludec) or adding another oral antidiabetic drug (sitagliptin) to the treatment regimen for people who are insulin naive and whose glycaemia is inadequately controlled with 1 or 2 oral antidiabetic drugs. Insulin degludec was superior to sitagliptin in terms of glycaemic control, but resulted in more episodes of overall confirmed hypoglycaemia. However, as insulin was titrated weekly in a treat-to-target approach, and the mean insulin dose increased throughout the trial, these results may be expected.

Like many studies of insulins, all 3 RCTs had an open-label design because the different delivery devices of insulin degludec and insulin glargine, and the fact that sitagliptin is given orally, 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 18% to 24% among participants randomised to insulin degludec, 16% to 23% among those randomised to insulin glargine and were 24% in those randomised to sitagliptin. 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 points of overall, nocturnal and (only on post-hoc analysis) daytime hypoglycaemia were statistically significantly reduced with insulin degludec compared with insulin glargine in BEGIN Basal-Bolus Type 2 (Garber et al. 2012). In BEGIN Once Long (Zinman et al. 2012), there

was no statistically significant difference between insulin degludec and insulin glargine in overall hypoglycaemia, but nocturnal and severe hypoglycaemia were statistically significantly reduced with insulin degludec compared with insulin glargine. However, these differences were small in absolute terms. There were reductions of about 2.5 episodes of overall hypoglycaemia, 0.5 episodes of nocturnal hypoglycaemia, and 2.1 episodes of daytime hypoglycaemia per patient per year of treatment in BEGIN Basal-Bolus Type 2; and reductions of 0.14 episodes of nocturnal hypoglycaemia in BEGIN Once Long. These results relate to self-treated, rather than severe, hypoglycaemic episodes.

The rates of severe hypoglycaemia were low in both trials, and because of this it was not possible to assess for statistically significant differences between groups in BEGIN Basal-Bolus Type 2. In BEGIN Once Long, a statistically significant reduction of 0.02 episodes of severe hypoglycaemia was reported with insulin degludec. However, this is based on very low numbers of just 2 episodes with insulin degludec and 5 episodes with insulin glargine.

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 people with type 2 diabetes can be provided by:

- NPH (isophane) insulin (for example, Insulatard, Humulin I or Insuman Basal) **or**
- the long-acting insulin analogues, insulin glargine (Lantus), insulin detemir (Levemir) or insulin degludec (Tresiba).

Costs of treatment alternatives

	5×3 ml cartridge (100 units/ml solution)	5×3 ml pre-filled pen (100 units/ml solution)
Insulatard	£22.90	£20.40
Humulin I	£19.08	£21.70
Insuman Basal	£17.50	£19.80

Insulin glargine (Lantus)	£41.50	£41.50
Insulin detemir (Levemir)	£42.00	£42.00
Insulin degludec (Tresiba)	£72.00	£72.00 (£86.40 for 3×3ml 200 units/ml solution)
Costs are excluding VAT; taken from MIMS July 2013.		

Estimated impact for the NHS

Likely place in therapy

The NICE clinical guideline on the management of type 2 diabetes (which is currently being updated; publication date to be confirmed) recommends that, when insulin therapy is necessary, human NPH (isophane) insulin is the preferred option. Examples of NPH (isophane) insulin include Insulatard, Humulin I or Insuman Basal. The guideline recommends that the long-acting insulin analogues, insulin glargine and insulin detemir, can be considered as an alternative in some people. This includes people who need assistance from a carer or healthcare professional to inject their insulin, people whose lifestyle is restricted by recurrent symptomatic hypoglycaemia, people who would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or those who cannot use the device to inject NPH insulin.

Based on the results of the studies by Garber et al. (2012) and Zinman et al. (2012), insulin degludec is likely to be marketed as a basal insulin for type 2 diabetes with potential benefits in reducing hypoglycaemia, particularly 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 differences in hypoglycaemic rates between insulin degludec and insulin glargine were statistically significant but small in absolute terms. 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 one 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 evidence review conducted for the NICE clinical guideline on type 2 diabetes: newer agents (NICE clinical guideline 87) found that there was no difference in terms of HbA_{1c} lowering between the long-acting insulin analogues available at that time (insulin glargine and insulin detemir) and NPH (isophane) insulin in type 2 diabetes. Compared with NPH (isophane) insulin, both these long-acting insulin analogues were associated with statistically significant reductions in the rates of any hypoglycaemia and of nocturnal hypoglycaemia, but not severe hypoglycaemia. The cost-effectiveness analysis conducted for the NICE clinical guideline on type 2 diabetes found that the long-acting insulin analogues, insulin glargine and insulin detemir, did not appear to be cost-effective options when compared with NPH (isophane) insulin in type 2 diabetes. All the incremental cost-effectiveness ratios (ICERs) were outside the conventional limits of cost effectiveness, with ICERs ranging from about £100,000 to £400,000 per quality-adjusted life year (QALY) gained depending on the scenario in which they are used. These are substantially greater than the £20,000 to £30,000 per QALY gained threshold usually considered in NICE's cost-effectiveness evaluations. Therefore, long-acting insulin analogues are only recommended for certain people with type 2 diabetes (see above).

Insulin degludec will be included in the update of the NICE clinical guideline on the management of type 2 diabetes. The publication date for this guideline is to be confirmed.

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 have defined the eligible population as adults (18 years or over) with type 2 diabetes currently on a basal long-acting insulin analogue (not basal NPH [isophane] insulin). Based on these estimates, for basal dosing in combination with oral antidiabetic drugs and for a population of 100,000 patients, this translates to the use of insulin degludec in 4 patients in year 1, 8 patients in year 2 and 12 patients in year 3. For use within a basal-bolus regimen, this translates to the use of insulin degludec in 7 patients in year 1, 14 patients in year 2 and 20 patients in year 3. This gives a total estimated uptake of 11 patients in year 1, 22 patients in year 2 and 32 patients in year 3 per 100,000 population (Novo Nordisk: personal communication August 2012).

Estimated usage in type 1 diabetes is given in the accompanying evidence summary on insulin degludec in type 1 diabetes.

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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

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