NHS
Herts Valleys
Clinical Commissioning Group

NHS
East and North Hertfordshire
Clinical Commissioning Group

HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC) - INSULIN DEGLUDEC (TRESIBA®) FOR THE TREATMENT OF DIABETES MELLITUS

RECOMMENDED FOR RESTRICTED USE – AMBER INITIATION

Name: generic (trade)	What it is	Indication	Decision last revised	Decision Status	NICE/SMC Guidance
Insulin degludec (Tresiba®)	Ultralong-acting insulin analogue	Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year as basal insulin therapy	Dec 2018	Final	NICE - No Guidance SMC – accepted for use in Type 1 and Type 2 diabetes in adults only

HMMC Recommendation (in line with East of England Priority Advisory Committee recommendations):

- **Insulin degludec (Tresiba®) is RECOMMENDED FOR RESTRICTED USE in certain patients with TYPE 1 OR TYPE 2 DIABETES FOLLOWING INITIATION BY A SPECIALIST** who fulfil the following criteria**:**
  - Patient with significant nocturnal hypoglycaemia, despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education, e.g. DAFNE, DESMOND), and optimisation of basal insulin/multiple daily injections.
  - "Chaotic patient" who may be at significant risk of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) (previously known as hyperosmolar non – ketotic diabetic state or hyper HONK) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.
  - Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA or HHS if daily basal insulin is missed.
  - Patients with a diagnosed allergy to either insulin glargine or insulin detemir.

Initiation, titration and stabilisation must be undertaken by consultants or consultant led specialist team. Once stabilised for continuation in primary care. Patients should be monitored and reviewed by the initiating specialist team within 6 months. Patients with significant nocturnal hypoglycaemia should demonstrate an objective evidence of improvement between pre- and 6-month post treatment and returned to previous treatment if no improvement in overall disease control from baseline is demonstrated.

Prescribing restricted to insulin degludec 100 units/ml strength to minimise any risk of error with the higher 200units/ml strength.

This **recommendation in relation to use in Type 2 diabetic patients is subject to a review in 12 months** based on local audit data from specialist teams on assessment of outcomes for patients started on degludec.

Insulin Degludec for diabetes prescribing support information for primary care is available on the following link https://hertsvalleysccg.nhs.uk/clinicians/medicines-guidance/topic/1049/Endocrine_system/541

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.

The East of England
Priorities Advisory Committee
A function of PrescQIPP

GUIDANCE STATEMENT

Insulin degludec (Tresiba®)

PAC recommendations

Recommendations for use in adults and children

1. Insulin degludec is not recommended for routine use in adults or children with either type 1 or type 2 diabetes.
2. Insulin degludec 100 units/ml may be of benefit in certain patients with type 1 or type 2 diabetes who fulfil the following criteria:
   - Patients with significant hypoglycaemia, despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education, e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy.
   - "Chaotic patients" who may be at significant risk of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) (previously known as hyperosmolar non – ketotic diabetic state or hyper HONK) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.
   - Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA or HHS if daily basal insulin is missed.
   - Patients with a diagnosed allergy to either insulin glargine or insulin detemir.
3. High strength insulin degludec 200 units/ml is not recommended for routine use. It should be considered for patients with severe insulin resistance requiring large daily doses of insulin (≥3 units/kg/day), where treatment is initiated by a Consultant Diabetologist in a tertiary centre specialising in insulin resistance.
4. Approval arrangements for treatment should be agreed locally. Following addition to local formularies, on-going assessment of treatment uptake should be monitored using ePACT data. It is also recommended that the commissioning decision is reviewed annually based on local audit and assessment of outcome data for patients started on insulin degludec to ensure that the treatment is continuing to meet the specific needs of the local population.
5. Insulin degludec should be initiated by a consultant Diabetologists only and is NOT suitable for initiation by GPs or other prescribers in primary care unless under the supervision of a specialist. It is recommended that the initial dose titration and monitoring is closely supervised by a specialist team.
6. All patients should be managed by the initiating specialist team for a minimum of three months or until stable. Patients should be returned to previous treatment if no improvement in overall disease control from baseline is demonstrated. Arrangements for the ongoing provision of the insulin in primary care should be agreed locally, ensuring that appropriate patient monitoring is in place.

Proposed sector of prescribing: Primary and secondary care

Key points

- Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia (high blood sugar) is caused by deficient insulin secretion or by resistance to the actions of insulin combined with relative insulin deficiency.
- Insulin degludec is an ultra-long-acting basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day, and should be dosed in accordance with the individual patient's needs.
- Insulin degludec has been shown to be non-inferior to insulin glargine 100 units/ml for both type 1 and type 2 diabetes. There are no superiority trials.
- There is limited comparative evidence with other insulins, including insulin glargine U300.
- There is limited evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions for diabetes related complications.
- There is no comparative evidence with insulin pumps.
- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is limited long-term safety data.
- Insulin degludec is available in two strengths, 100 units/ml and 200 units/ml. The latter strength is classified as high strength insulin and may be associated with an increased risk of medication errors, due to the wrong product being supplied. An MHRA Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths. The use of high strength insulins is not routinely supported.
- The East of England Priorities Advisory Committee remain concerned regarding the level provision of adequate monitoring and support available to prescribers in primary care and the overall management of high risk and/or complicated diabetic patients in primary care.
- NICE Evidence Summaries are available for insulin degludec. There are no technology appraisals (TAs) for insulin degludec. Insulin degludec is not in the NICE TA work programme.
- The NICE Clinical Guideline for type 2 diabetes (NG28) recommends isophane (NPH) insulin including biphasics, as first line treatment for patients who remain uncontrolled despite optimised treatment with oral hypoglycaemics. Basal analogue insulins are only recommended second line to NPH insulins and there is no specific recommendation in relation to the use of insulin degludec in the type 2 clinical guideline.
- The NICE Clinical Guideline on type 1 diabetes in adults (NG17), makes no specific recommendation on the use of insulin degludec, however it does suggest that basal insulin other than insulin glargine or insulin determir could be considered in patients where agreed targets are not being met. The clinical guidance for the management of diabetes in children does not include any discussion regarding insulin degludec.
- The Scottish Medicines Consortium (SMC) have approved insulin degludec for use in adults but not in adolescents and children as it has not yet considered its use in these patient groups.
- Insulin degludec is recommended as an option for restricted use within NHS Wales for the treatment of diabetes mellitus in adult patients where treatment with a basal insulin analogue is considered appropriate. It is not recommended for use in adolescents and children from the age of one year.
- Insulin degludec has a higher cost than biphasic insulin or other long acting basal insulins. In clinical trials, insulin degludec was started at a dose of 10 units/day in insulin naïve patients,

with a mean insulin degludec dose of 30 units per day. Patients on alternative insulins were transferred on a unit to unit basis. The current cost for biphasic insulin is approximately £30 per pack, or £0.41 for 30 units and £150 per year, based on 30 units per day; for insulin glargine (long acting basal insulin) the cost is £0.83 for 30 units and £302.12 per year, versus £0.93 for 30 units or £339.25 per year for insulin degludec.

- Insulin degludec may offer few or no meaningful advantages for the majority of potential users but may be suitable for a small subgroup of patients for whom glycaemic control cannot be achieved despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy, or individuals for whom injecting at the same time every day may not always be possible.
- In these groups of patients, the use of insulin degludec could be considered to be cost neutral or more cost effective when compared with other treatment options.

Introduction

Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia is caused by deficient insulin secretion, or by resistance to the actions of insulin, often combined with relative insulin deficiency. Insulin deficiency and insulin resistance leads to the abnormalities of carbohydrate, fat, and protein metabolism that are characteristic of diabetes mellitus.[1,2]

Insulin degludec is an ultra-long-acting basal analogue insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation. This leads to a flat and stable glucose-lowering effect.[3-5]

Insulin degludec has a cited duration of action between 36 and 42 hours[3-5] with a half-life of approximately 25 hours independent of dose.[4]

Type 1 diabetes

In SWITCH 1,[6] a double blind, randomised, crossover, non-inferiority trial, 501 adults with at least one hypoglycaemia risk factor, were randomised 1:1 to receive once daily insulin degludec (n=252) for 32 weeks, followed by insulin glargine for 32 weeks or insulin glargine U100 followed by insulin degludec (n=249). The primary endpoint was the rate of overall severe or blood glucose confirmed symptomatic hypoglycaemia (<56mg/dl or < 3.1mmol/l) episodes during the maintenance period. Of the 501 patients (mean age 45.9 years) who were randomised, 395 patients completed the trial. Reasons for discontinuation included discontinued early (no additional reason given), adverse event, hypoglycaemia, lost to follow up, protocol violations, or withdrawal by patient. The number of patients who discontinued for each reason was similar in both treatment groups.

During the maintenance period, the rates of overall symptomatic hypoglycaemia were lower in the insulin degludec group versus the insulin glargine U100 group; 2200.9 episodes per 100 person-years (PYE) versus 2462.7 episodes per 100 PYE [rate ratio (RR) 0.89; 95% CI 0.85-0.94; p<0.001 for non-inferiority]. The rate difference was -130.21 episodes per 100 PYE.

The rates of nocturnal hypoglycaemia were 277.1 per 100 PYE in the insulin degludec group versus 428.6 episodes per 100 PYE in the glargine group [RR 0.64; 95% CI 0.56-0.73; p<0.001 for non-inferiority]. The rate difference was -61.94 episodes per 100 PYE; 95% CI -83.85 to -40.03.[6]

Two open-label, phase 3, non-inferiority trials have also compared insulin degludec with insulin glargine once daily.[7,8] In the first trial,[7] 629 patients who had been treated with basal bolus insulin for at least a year and with a HbA1c level of 61-86mmol/mol (7.7%-10%), received either insulin glargine or insulin degludec once daily. Insulin aspart was used at mealtimes. The primary outcome measure was the mean decrease in HbA1c. Treatment was titrated to achieve plasma glucose control between 3.9-5.0mmol/L. After 52 weeks, mean decreases of 4.3-4.4 mmol/mol (0.39% and 0.49%) were recorded in the insulin glargine and insulin degludec groups respectively (p<0.0001).[7]

In the second trial,[8] 493 patients were split into three groups to receive either insulin degludec administered at a variable interval of between eight to 40 hours or insulin degludec at the same time each day or insulin glargine 100units/ml given at a fixed time each day for 26 weeks. The mean HbA1c decreased by 4.4mmol/mol (0.4%) with the variable regime and 4.5 mmol/mol (0.41% and 0.58%), for the insulin degludec and insulin glargine fixed time groups respectively. Nocturnal hypoglycaemia was assessed as a secondary endpoint in both trials and was reported as lower in patients being treated with insulin degludec vs. insulin glargine in trial 1 but not in trial 2.[8] The overall clinical significance of this is unclear.

Children

In a 26-week, randomised open label, parallel group, non-inferiority trial, 350 children aged between one and 17 years with type 1 diabetes received either insulin degludec once daily (n=174) or insulin detemir (n=176) once or twice daily. Both groups received mealtime insulin aspart. After the initial 26 weeks 280 patients entered a 26 week extension phase. The primary endpoint was change in baseline in Hb1Ac after 26 weeks' treatment.[9]

Non-inferiority was confirmed with respect to change in baseline for Hb1Ac; estimated treatment difference (ETD) 0.15% [0.03; 0.32]. At 52 weeks, HbA1c was 7.9% with insulin degludec vs. 7.8% with insulin detemir. The majority of insulin detemir treated patients required twice daily administration to achieve glycaemic targets. Overall hypoglycaemia rates did not differ significantly between degludec and detemir, however, nocturnal hypoglycaemic rates were lower in the degludec group, but serious hypoglycaemic episodes occurred more frequently. Rates of hyperglycaemia with ketosis were lower in those treated with insulin degludec vs. insulin detemir.[9]

Type 2 diabetes

In SWITCH 2,[10] a double blind, randomised, crossover trial, 721 adults with type 2 diabetes and at least 1 hypoglycaemia risk factor and who were previously treated with basal insulin, were randomised 1:1 to receive once daily insulin degludec (n=361) for 32 weeks, followed by insulin glargine for 32 weeks or insulin glargine U100 followed by insulin degludec (n=360). The primary end point was the rate of overall symptomatic hypoglycaemia episodes (severe or blood glucose confirmed; <56mg/dl or < 3.1mmol/l), during the maintenance period. Of the 721 patients who were randomised, 580 (80.4%) completed the trial. During the maintenance period, the rates of overall symptomatic hypoglycaemia for insulin degludec vs. insulin glargine U100 were 185.6 vs. 265.4 episodes per 100 PYE; [RR 0.70; 95% CI 0.61-0.80; p<0.001], with a between treatment difference of -23.66 episodes/PYE; 95% CI -33.98 to -13.33. The rates of nocturnal symptomatic hypoglycaemia with insulin degludec vs. insulin glargine U100 were 55.2 versus 93.6 episodes/100 PYE; [RR 0.58; 95% CI -0.46 to 0.74: p<0.001]. The between treatment difference was -7.41 nocturnal hypoglycaemia episodes/00 PYE; [95% CI -11.98 to -2.85].[10]

Two phase-3, open-label, trials, investigated the non-inferiority of insulin degludec compared to insulin glargine 100units/ml in patients with type 2 diabetes previously treated with insulin.[11,12]

In the first trial,[11] 1,006 patients with inadequate HbA1c control despite treatment with insulin (with or without oral antidiabetic drugs) for at least three months were randomised to receive either insulin degludec or insulin glargine 100units/ml. Metformin or pioglitazone were permitted during the trial. The primary end point was reduction in HbA1c at three months.

At three months the study reported that non-inferiority was proven by the reduction in HbA1c level of 12.1mmol/mol (1.1%) for insulin degludec versus 13mmol/mol (1.18%) for insulin glargine 100units/ml. Rates of nocturnal hypoglycaemia were 40% vs. 47% resulting in 0.5 fewer episodes per year per patient for insulin degludec.[11]

In the second trial,[12] 687 patients with either type 1 or type 2 diabetes received either insulin glargine 100units/ml or insulin degludec administered at a variable dose interval of 8-40 hours or a fixed time interval. Both insulin naïve and patients with prior insulin use were included. The primary outcome was the mean change in HbA1c. After 52 weeks, a decrease in HbA1c of 14mmol/mol (1.28%) was seen for

insulin degludec (variable injection time), 11.8mmol/mol (1.07%) for insulin degludec (fixed time) and 13.9mmol/mol (1.26%) for the insulin glargine 100units/ml group (fixed time), and the investigators concluded that non-inferiority had been demonstrated.[12] Rates of severe hypoglycaemia were similar between those treated with insulin degludec or insulin glargine 100units/ml.[12]

In DEVOTE, a double blind, treat to target, non-inferiority study, 7637 patients with type 2 diabetes were randomly assigned to receive either insulin degludec (n=3818) or insulin glargine U100 (n=3819) once daily.[13] The primary outcome was the first occurrence of an adjudicated major cardiovascular event, however the trial also included efficacy measures as a secondary outcome. At 24 months, the mean glycated haemoglobin level was 7.5±1.2% in each group, however the mean fasting plasma glucose level was significantly lower in the degludec group than the glargine group (128±56 vs 136±57mg/dl; p<0.001). Severe hypoglycaemia occurred in 187 patients (4.9% in the degludec group and 252 (6.2%) in the glargine group) with an absolute difference of 1.7 percentage points [RR 0.60; p<0.001).[13]

Adverse events

The adverse events reported in the trials were generally similar between insulin glargine U100 and insulin degludec.[4,14] The European Medicines Agency (EMA) approved degludec in September 2012, but the US FDA have only recently granted approval to insulin degludec and insulin degludec plus aspart. This was due to a possible increased risk of cardiovascular events in patients being treated with insulin degludec.[15] The FDA therefore asked the manufacturer to conduct further cardiovascular safety studies (DEVOTE study). In support of their opinion, the FDA cited a meta-analysis of studies which calculated that degludec increased the risk of major adverse cardiovascular events (hazard ratio 1.67, 95% CI 1.01 to 2.75) as the reason for its decision at the time. Whilst the same data was available to the EMA in September 2012, the EMA used a different interpretation of events in the pre-specified analysis used during the product assessment process, which calculated the hazard ratio for major cardiovascular events as 1.097 (0.681 to 1.768).[16] The results of a trial comparing the incidence of major cardiovascular events during therapy with insulin degludec versus insulin glargine in people with type 2 diabetes at high risk of cardiovascular events have recently been published. In DEVOTE, a double blind, treat to target, non- inferiority study, 7637 patients with type 2 diabetes were randomly assigned to receive either insulin degludec (n=3818) or insulin glargine U100 (n=3819) once daily.[13] The primary composite outcome in the time to event analysis was the first occurrence of an adjudicated major cardiovascular event with a pre-specified non- inferiority margin of 1.3. The primary outcome occurred in 325 (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio 0.91; 95% confidence interval 0.78 to 1.06; p<0.001 for non-inferiority). The study authors concluded that in patients with type 2 diabetes at high risk of cardiovascular events, degludec was non-inferior to glargine U100.[13] Severe hypoglycaemia occurred in 187 patients (4.9% in the degludec group and in 252 patients (6.6%) in the glargine group). Rates of other adverse events did not differ significantly between the groups.

Evidence strengths and limitations

- Insulin degludec has been shown to be non-inferior to insulin glargine 100units /ml. There are no superiority trials.
- There is some comparative evidence with insulin glargine U100 and limited comparative evidence with other insulins. There are no trials comparing it to Neutral Protamine Hagedorn (NPH) insulin or insulin glargine U300 (Toujeo®)
- There is no evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions for diabetes related complications.
- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is limited long-term safety data.
- There is no evidence which directly compares insulin degludec with insulin pumps.

National and local guidance and decisions

NICE Evidence Summaries are available for insulin degludec.[17,18] There are no technology appraisals (TAs) for insulin degludec. Insulin degludec is not in the NICE TA work programme. The NICE Clinical Guideline for type 2 diabetes (NG28) recommends isophane (NPH) insulin including biphasics, as first line treatment for patients who remain uncontrolled despite optimised treatment with oral hypoglycaemics. Basal analogue insulins are only recommended second line to NPH insulins and there is no specific recommendation in relation to the use of insulin degludec in the type 2 clinical guideline.[19] The full version of this guideline also states that the guideline development group considered that, insulin degludec could not be recommended as it was not cost effective; however, it should be noted that this guidance was produced before the recent price reduction of insulin degludec.[19]

The NICE Clinical Guideline on type1 diabetes in adults (NG17) makes no specific recommendation on the use of insulin degludec however the full guideline notes that insulin degludec is currently priced at a much higher level than both insulin detemir and insulin glargine with no evidence of improved effectiveness, and hence, it is currently dominated by both of them, but suggests that it could be an option in patients who are currently receiving this treatment with satisfactory results or in patients for whom other insulins are not showing any effectiveness.[20] The clinical guidance for the management of diabetes in children does not include any discussion regarding insulin degludec.[21]

The Scottish Medicines Consortium (SMC) have approved insulin degludec for use in adults, but not in adolescents and children as it has not yet considered its use in these patient groups.[22]

Insulin degludec (Tresiba®) is recommended as an option for restricted use within NHS Wales for the treatment of diabetes mellitus in adult patients where treatment with a basal insulin analogue is considered appropriate. Insulin degludec (Tresiba®) is not recommended for use within NHS Wales for the treatment of diabetes mellitus in adolescents and children from the age of one year.[23]

Place in therapy

Insulin degludec may offer few or no meaningful advantages for the majority of potential users but may be suitable for a small subgroup of patients, for whom glycaemic control cannot be achieved despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education, e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy, or for individuals for whom injecting at the same time every day may not always be possible.

It has been suggested that insulin degludec may be an alternative to other insulins in patients with uncontrolled diabetes and experiencing multiple emergency admissions for hypoglycaemia and/or diabetic ketoacidosis, who would otherwise require treatment with an insulin pump or would continue to experience frequent hospital admissions. The number of likely patients with unstable diabetes who may benefit from a trial of insulin degludec is small and unstudied.

The use of the higher strength insulin degludec 200units/ml is not routinely recommended, but could be considered in patients receiving large daily doses (≥3units/kg/day)[24] following referral to tertiary centre for severe insulin resistance, where treatment is initiated by a Consultant Diabetologist.

Comparative Costs (October 2017) and eBNF)

Until recently, insulin degludec was the highest cost insulin available. From the 1st July 2016, Novo Nordisk announced a significant price reduction, and the cost of insulin degludec is now more comparable to other similar insulins, including insulin glargine U300 (Toujeo®).[25] Insulin degludec has a higher cost than biphasic insulin or other long acting basal insulins. In clinical trials, insulin degludec was started at a dose of 10 units/day in insulin naïve patients, with a mean insulin degludec dose of 30 units per day. Patients on alternative insulins were transferred on a unit to unit basis. The current cost for biphasic insulin is approximately £30 per pack, or £0.41 for 30 units and £150 per year, based on 30 units per day;

for insulin glargine (long acting basal insulin) the cost is £0.83 for 30 units and £302.12 per year versus £0.93 for 30 units and £339.25 per year for insulin degludec.

Comparative costs of all the insulins are shown in table 1.[25-27] Information regarding basic pharmacokinetics details of the different insulins has been included in table 2 in Appendix 1.

Table 1: Comparative costs for long acting basal analogue insulins (October 2017 eMIMs and eBNF)

Brand name		Generic name	Cost per pack	Cost per unit	Cost for 30 units	Cost per 28 days	Cost per year
Basal insulin	Humulin I	Isophane insulin (NPH insulin)	£21.70	£0.014	£0.43	£12.18	£158.00
	Insulatard	Isophane Insulin (NPH insulin)	£20.40	£0.014	£0.41	£11.42	£148.51
	Insuman Basal	Isophane Insulin (NPH insulin)	£19.80	£0.013	£0.40	£11.09	£144.14
Basal - insulin analogues	Lantus	Insulin glargine U100	£41.50	£0.03	£0.83	£23.24	£302.12
	Abasaglar	Insulin glargine - biosimilar U100	£35.28	£0.02	£0.71	£19.76	£256.84
	Levemir	Insulin determir	£42.00	£0.03	£0.84	£23.52	£305.76
Basal - ultra long acting insulin analogues	Tresiba	Insulin degludec U100	£46.60	£0.03	£0.93	£26.10	£339.25
High strength basal insulin (Concentrated)	Toujeo	Insulin glargine U300	£33.13	£0.02	£0.80	£22.40	£291.20
	Tresiba	Insulin degludec U200	£55.92	£0.03	£0.93	£26.10	£339.25
	Humulin R (imported from US- unlicensed in UK)	Insulin human injection, USP				£211*	£274
Biphasic or Premixed Insulins	Humulin M3 70/30	Insulin NPH + neutral insulin	£21.70	£0.014	£0.43	£12.18	£158.00
	Humalog Mix	Insulin lispro + insulin lispro protamine	£29.46	£0.02	£0.59	£16.50	£214.47
	Novomix 30	Insulin aspart + insulin aspart protamine	£28.79	£0.02	£0.58	£16.12	£209.59
	Insuman Comb	Neutral insulin + isophane insulin	£19.80	£0.013	£0.40	£11.09	£144.14

Insulin degludec is included in the PbR tariff.[28]

The table shows the cost per year based on 30 units per day. In clinical trials, degludec was started at a dose of 10 units/day in insulin naïve patients.

The mean average number of units of once daily degludec at the end of the BEGIN trial was approximately 24.5 units per day in type 1 patients and 45 units per day in type 2 patients based on a 70kg adult.[7, 11]

For patients switching from other basal insulins, the SPC for insulin degludec now recommends the following: a dose reduction of 20% based on the previous basal insulin dose followed by individual dosage adjustments should be considered when:

- Transferring to Tresiba® from twice-daily basal insulin
- Transferring to Tresiba® from insulin glargine (300 units/mL).[4]

Insulin degludec is available as cartridges (100units/ml) and as a pre-filled pen (Flex-Touch) which is available in two strengths (100 units/ml and the higher strength 200 units/ml). Both prefilled pens dial the dose in the number of units, which mitigates the risk of the incorrect number of doses being given.[4] Estimated activity costs for an uncontrolled diabetic experiencing hypoglycaemic episodes resulting in at least one hospital admission per month is approximately £18,000 per year.[28]

Implementation considerations

Insulin degludec (Tresiba®) is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of one year.[4] Insulin glargine U300 (Toujeo), which has a similar pharmacokinetic profile to insulin degludec is only currently licensed in adults.[29]

Insulin degludec is available as both standard strength (100units/ml) and a higher strength (200 units/ml) formulations.[4] The use of higher strength insulins is not routinely supported, due to a possible increased risk of medication errors.[30]

The availability of higher strength insulin products has been associated with a possible increase risk of medication errors. The strength of the insulin formulation should always be included on the prescription. A Medicines and Healthcare Regulatory Agency (MHRA) Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths, including risk assessment of clinical storage areas.[30,31]

The EMA has also published guidance to prevent medication errors with high strength insulins, including a series of recommendations for health care professionals.[32] Education and awareness of the risks of high strength and high dose insulin amongst healthcare professionals, patients and their carers is essential to ensure patient safety and to minimise the risk posed by these formulations. For the higher strength insulins, patients and carers should be advised to only administer the insulin via the pen device and to not tamper with the device to enable administration with needles and syringes, as this could lead to the wrong dosage being administered.[32]

The East of England Priorities Advisory Committee remain concerned regarding the level provision of adequate monitoring and support available to prescribers in primary care and the overall management of high risk and/or complicated diabetic patients in primary care.

All healthcare professionals are reminded of the need for extra vigilance when prescribing, dispensing and using both long-acting and/or high strength insulins, including checking directly with the patient at the point of supply, the brand, formulation and strength of insulin they are expecting and the practicalities with respect to storage of the insulins in all pharmacies, to minimise the potential for dispensing and medication supply errors.[30-33]

In 2011, following a review of 16,600 patient safety incidents involving all insulins, reported to the National Reporting and Learning System (NRLS) over a six-year period, between 1 November 2003 and 1 November 2009, the National Patient Safety Agency (NPSA) made several, recommendations to improve the safety of insulin use.[33] Over the course of the review, six deaths and 12 incidents resulting in

severe harm were reported. Of the 16,600 incidents, 26% were due to the wrong insulin dose, strength or frequency and 20% were due to omitted medicine. Patients being prescribed or dispensed the wrong insulin product accounted for 14% of incidents.[33] One of the measures initiated to mitigate this risk, was the introduction of the insulin passport to record the dose and brand on insulin, which is retained by the patient.

The EMA advise, that when switching patients from standard-strength insulin to another insulin formulation which is not bioequivalent, switching can be done on a unit to unit basis, but the dose may need to be adjusted to achieve target ranges for plasma glucose level. More detailed information on dose adjustment is provided in the product information.[32] However as with all insulin switches, there is great variability in the absorption and action of insulin in different patients and dose adjustment may be needed when patients are switched from insulin glargine U100 (Lantus®) or other basal insulins to insulin degludec® or vice versa.[30-33] All patients should be closely monitored, particularly at the start of treatment and when the dose or type of insulin changes.[32] Initial and subsequent dose titration and monitoring should take place under the close supervision of a specialist team.

*Consult Summary of Prescribing Characteristics for full prescribing details.

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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Document history

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Consultation process	PAC members East of England clinicians		
QA process	Katie Smith, Senior Clinical Pharmacist, PrescQIPP - 19 February 2018		

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Search strategy

The following databases were searched: NHS evidence, Embase, Medline via Pubmed and Athens, and Biomed Central. Search terms used were degludec, glargine, Tresiba, Lantus, alone and in combination.

Appendix 1. Comparative data

Table 2. Comparative pharmacokinetics of insulins

Brand name		Generic name	Onset	Peak	Duration
Bolus insulin	Actrapid	Soluble or neutral insulin	<30min	1.5-3.5	7-8hr
	Humulin S	Soluble or neutral insulin	30min-1hr	1-6hr	6-12hr
	Insuman Rapid	Soluble or neutral insulin	<30min	1-4hr	7-9h
Rapid acting-bolus insulin	Novorapid	Insulin aspart	10-20min	1-3hr	3-5hr
	Humalog	Insulin lispro	15min	1.5hr	2-5hr
	Fiasp	Insulin aspart	4min	1-3hr	3-5hr
	Apidra	Insulin glulisine	10-20 min	55 min	1.5-4hr
Basal insulin	Humulin I	Isophane insulin (NPH insulin)	30min-1hr	1-8hr	22hr
	Insulatard	Isophane insulin (NPH insulin)	<1.5hr	4-12hr	24hr
	Insuman basal	Isophane insulin (NPH insulin)	<1hr	3-4hr	11-20hr
Basal - insulin analogues	Lantus	Insulin glargine U100	1-4hr	-	24hr
	Abasaglar	Insulin glargine - biosimilar U100	1-4hr	-	24hr
	Levemir	Insulin determir	30min-1hr	-	24hr
Basal - ultra long acting insulin analogues	Tresiba	Insulin degludec U100	1-2hr	-	>42hr
High strength basal insulin (concentrated)	Toujeo	Insulin glargine U300	1-6hr	-	24-36hr
	Tresiba	Insulin degludec U200	1-2hr	-	>42hr
	Humulin R (Imported from US- unlicensed in UK)	Insulin human injection, USP	30-45min	4-8hr	12-24hr
Biphasic or premixed insulins	Humulin M3 70/30	Insulin NPH + neutral insulin	30min-1hr	1-12hr	22hr
	Humalog Mix	Insulin lispro+ insulin lispro protamine	15min	2hr	22hr
	Novomix	Insulin aspart + insulin aspart protamine	10-20 min	1-4hr	24hr
	Insuman Comb	Neutral insulin + isophane insulin	30min-1hr	2-4hr	11-20hr

Appendix 2: Assessment against ethical and commissioning principles

Treatment assessed

Insulin degludec (Tresiba®)

East of England Priorities Advisory Committee Recommendation

Insulin degludec is not recommended for routine use in adults or children with either type 1 or type 2 diabetes.

Insulin degludec 100 units/ml may be of benefit in certain patients with type 1 or type 2 diabetes who fulfil the following criteria:

- Patient with significant hypoglycaemia, despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy.
- "Chaotic patient" who may be at significant risk of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) (previously known as hyperosmolar non – ketotic diabetic state or hyper HONK) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.
- Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA or HHS if daily basal insulin is missed.
- Patients with a diagnosed allergy to either insulin glargine or insulin detemir.
- High strength insulin degludec 200 units/ml is not recommended for routine use. It should be considered for patients with severe insulin resistance requiring large daily doses of insulin (≥3units/kg/day), where treatment is initiated by a Consultant Diabetologist in a tertiary centre specialising in insulin resistance.
- Approval arrangements for treatment should be agreed locally. Following addition to local formularies, on-going assessment of treatment uptake should be monitored using ePACT data. It is also recommended that the commissioning decision is reviewed annually based on local audit and assessment of outcome data for patients started on insulin degludec to ensure that the treatment is continuing to meet the specific needs of the local population.
- Insulin degludec should be initiated by a consultant Diabetologists only and is NOT suitable for initiation by GPs or other prescribers in primary care unless under the supervision of a specialist. It is recommended that the initial dose titration and monitoring is closely supervised by a specialist team.
- All patients should be managed by the initiating specialist team for a minimum of 3 months or until stable. Patients should be returned to previous treatment if no improvement in overall disease control from baseline is demonstrated. Arrangements for the ongoing provision of the insulin in primary care should be agreed locally, ensuring that appropriate patient monitoring is in place.

Clinical effectiveness

- Insulin degludec has been shown to be non-inferior to insulin glargine 100units /ml. There are no superiority trials.
- There is some comparative evidence with insulin glargine U100 and limited comparative evidence with other insulins. There are no trials comparing it to Neutral Protamine Hagedorn (NPH) insulin or insulin glargine U300 (Toujeo®).

- In SWITCH 1, a double blind, randomised, crossover, non-inferiority trial, 501 adults with at least 1 hypoglycaemia risk factor, were randomised 1:1 to receive once daily insulin degludec (n=252) for 32 weeks, followed by insulin glargine for 32 weeks or insulin glargine U100 followed by insulin degludec (n=249). The primary endpoint was the rate of overall severe or blood glucose confirmed symptomatic hypoglycaemia (<56mg/dl or < 3.1mmol/l) episodes during the maintenance period. During the maintenance period, the rates of overall symptomatic hypoglycaemia were lower in the insulin degludec group versus the insulin glargine U100 group; 2200.9 episodes per 100 person-years' (PYE) versus 2462.7 episodes per 100 PYE. [rate ratio 0.89; 95% CI 0.85-0.94; p<0.001 for non-inferiority]. The rate difference was -130.21 episodes per 100 PYE; 95% CI -193.5 to -67.16.
- The rates of nocturnal hypoglycaemia were 277.1 per 100 PYE in the insulin degludec group versus 428.6 episodes per 100 PYE in the glargine group [RR 0.64; 95% CI 0.56-0.73; p<0.001 for non-inferiority]. The rate difference was -61.94 episodes per 100 PYE; 95% CI -83.85 to -40.03.
- In SWITCH 2, a double blind, randomised, crossover trial, 721 adults with type 2 diabetes and at least 1 hypoglycaemia risk factor and who were previously treated with basal insulin, were randomised 1:1 to receive once daily insulin degludec (n=361) for 32 weeks, followed by insulin glargine for 32 weeks or insulin glargine U100 followed by insulin degludec (n=360). The primary end point was the rate of overall symptomatic hypoglycaemia episodes (severe or blood glucose confirmed; <56mg/dl or <3.1mmol/l). During the maintenance period, the rates of overall symptomatic hypoglycaemia for insulin degludec vs. insulin glargine U100 were 185.6 vs. 265.4 episodes per 100 PYE; [RR 0.70; 95% CI 0.61-0.80; p<0.001], with a between treatment difference of -23.66 episodes/100 PYE; 95% CI -33.98 to -13.33. The rates of nocturnal symptomatic hypoglycaemia with insulin degludec vs. insulin glargine U100 were 55.2 versus 93.6 episodes/100 PYE; [RR 0.58; 95%CI, -0.46 to 0.74: p<0.001]. The between treatment difference was -7.41 nocturnal hypoglycaemia episodes/100 PYE; [95% CI -11.98 to -2.85].
- Several open label studies have also been conducted which assessed the non-inferiority of insulin degludec compared with insulin glargine U100.
- There is no evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions for diabetes related complications.
- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is limited long-term safety data.
- There is no evidence which directly compares insulin degludec with insulin pumps.

Cost effectiveness

There is little to no cost effectiveness data available with respect to insulin degludec.

It is unknown if savings would be realised if patients with sub-optimally controlled type 1 diabetes who qualify for pump therapy received insulin degludec and subsequently did not require pump therapy or if the number of repeat admissions for diabetic ketoacidosis in patients treated with insulin degludec would be reduced as this has not been studied.

There is limited data available on which to base an accurate assessment of likely patient numbers who would be eligible for treatment. It has been estimated from local data that approximately one patient per 100,000 populations could be eligible for treatment due to unstable or brittle diabetes resulting in multiple hospital readmissions and in line with the suggested start criteria. The average activity cost per year per patient is approximately £18,000 based on one admission per month for 12 months. There is no trial data to confirm the effect, if any, on hospital admissions with either strength of insulin degludec.

However, assuming that 10 patients are admitted to hospital five times per year with an average spell cost of £1,500; the total cost of hospital treatment for one year will be £75,000 for these 10 patients. The cost of treating all 10 patients with insulin degludec for one year, (30-40 units daily) would be £3,390-£4,520. If one patient was successfully treated with insulin degludec (no hospital admissions) then the annual saving for one patient could be approximately £7,000 per patient per year. (i.e. if 10 patients were successfully treated, then the annual potential cost saving could be approximately £70,000 per year for these ten patients).

For a small subgroup of patients, for whom glycaemic control cannot be achieved despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy or individuals for whom injecting at the same time every day may not always be possible, the use of insulin degludec could be considered to be cost neutral or more cost effective when compared with other treatment options.

Equity

No issues identified.

Needs of the community

The needs of the community are considered moderate. The use of ultra-long acting insulins such as insulin degludec or insulin glargine U300, instead of alternatives would create a cost pressure which may have an impact on the local health economy which already has to identify savings. Any potential savings from the use of insulin degludec are unknown at this stage.

Need for healthcare

The needs of the population appear to be low as there are available alternative treatment options recommended within local guidelines and by NICE. However, specialists have highlighted a cohort of patients with sub-optimal control who may benefit from treatment with Insulin degludec or insulin glargine U300®.

For discussion regarding risks and benefits of high strength insulin products see safety section.

Policy drivers

Safety issues with high strength need to be carefully considered.

Disinvestment

Insulin Glargine U300 (Toujeo®) is a possible treatment alternative to Humulin R (insulin U500) in patients with extreme insulin resistance.