BEDFORDSHIRE, LUTON AND MILTON KEYNES AREA PRESCRIBING COMMITTEE (BLMK APC)

Insulin degludec (Tresiba®)

The APC agreed to support the Updated East of England Priorities Advisory Committee (EoEPAC) Guidance Statement (attached) with a locally modified set of recommendations.

(Previous version – Approved by the Bedfordshire and Luton Joint Prescribing Committee (JPC) November 2018)

Approved: March 2023
Review: March 2026

The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Integrated Care Board; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust

Bedfordshire, Luton and Milton Keynes Health and Care Partnership

NHS

BLMK Area Prescribing Committee Recommendations (local agreement):

1. Insulin degludec is not recommended for routine use in children with type 1 or type 2 diabetes.
2. Updated NICE guidance regarding the management of type 1 diabetes in adults recommends insulin degludec 100 units/ml as an alternative to twice daily insulin detemir or once daily insulin glargine 100 units/ml, for patients where nocturnal hypoglycaemia is a particular concern or for people who need help from a carer or healthcare professional to administer injections.
3. In addition, the East of England Priorities Advisory Committee (EoE PAC) considers that insulin degludec 100 units/ml may also be of benefit in certain patients with type 1 or type 2 diabetes who fulfil the following criteria and where insulin detemir and insulin glargine have been tried, or are not clinically suitable:
    - 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.
    - People with erratic lifestyles who may be at significant risk of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) (previously known as hyperglycaemic hyperosmolar non–ketotic diabetic coma or 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.
4. High strength insulin degludec 200 units/ml is not recommended for routine use. It should only be considered for patients with severe insulin resistance requiring large daily doses of insulin (≥3units/kg/day), where treatment is initiated by the Specialist Diabetes Service.
5. In all the above situations, insulin degludec (Tresiba®) should be initiated by the Specialist Diabetes Service only and is not suitable for initiation by GPs or other prescribers in primary care unless under the supervision of a specialist. For insulin degludec 200 units/ml, it is recommended that the initial dose titration and monitoring is closely supervised by a specialist team.
6. Insulin degludec 100 units/ml is recommended for specialist initiation/ recommendation with GP continuation. Patients should be returned to their previous treatment if no improvement in overall disease control from baseline is demonstrated.

7. Insulin degludec 200 units/ml: All patients should be managed by the initiating specialist team until the patient is stable (usually a minimum of 3 months). After this time period, prescribing may be transferred to the GP assuming that the patient is stable. Patients should be returned to their previous treatment if no improvement in overall disease control from baseline is demonstrated.
8. 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.
9. These recommendations will be reviewed in the light of new evidence on clinical, cost effectiveness and safety.

NB: The full EoEPAC document is attached however clinicians should note that the APC recommendations outlined above replace the EoEPAC recommendations.

The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Insulin degludec (Tresiba®)

PAC recommendations for use in adults and children

1. Insulin degludec is not recommended for routine use in children with type 1 or type 2 diabetes.
2. Updated NICE guidance regarding the management of type 1 diabetes in adults recommends insulin degludec 100 units/ml as an alternative to twice daily insulin detemir or once daily insulin glargine 100 units/ml, for patients where nocturnal hypoglycaemia is a particular concern or for people who need help from a carer or healthcare professional to administer injections.
3. In addition, the East of England Priorities Advisory Committee (EoE PAC) considers that insulin degludec 100 units/ml may also be of benefit in certain patients with type 1 or type 2 diabetes who fulfil the following criteria and where insulin detemir and insulin glargine have been tried, or are not clinically suitable:
   - 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 hyperglycaemic hyperosmolar non–ketotic diabetic coma or 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.
4. High strength insulin degludec 200 units/ml is not recommended for routine use. It should only 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.
5. 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.
6. 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.
7. 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.

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 with respect to changes in HbA1c for up to two years. There are no superiority trials.
- There is some limited comparative evidence with other insulins, including insulin glargine 300 units/ml and limited published data beyond two years.
- The adverse events reported in the trials were generally similar between insulin glargine 100 units/ml and insulin degludec.
- From the trial data to date, insulin degludec may be associated with lower rates of severe hypoglycaemia and nocturnal hypoglycaemia than insulin glargine 100 units/ml.
- Data from head-to-head trials comparing insulin degludec 100 units/ml directly with insulin glargine 300 units/ml showed similar but very small changes in Hb1Ac and other measures of glycemic control with both treatments. Further data is required, particularly in relation to the comparative differences if any, of insulin degludec 100 units/ml and insulin glargine 300 units/ml on hypoglycaemia incidence and event rate. Whilst data to date appears to suggest lower rates of hypoglycaemia with insulin degludec, results between trials and subgroups are inconsistent and conflicting. More data is required.
- There is limited published evidence to confirm that insulin degludec use is associated with a reduction in hospital admissions or emergency department/service encounters for diabetes related complications. More data is required.
- There are no patient-oriented outcome data for the effects of insulin degludec on macrovascular or microvascular outcomes.
- There is no evidence which directly compares insulin degludec with subcutaneous insulin pumps with/without continuous glucose monitoring.
- 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.
- EoE PAC remains 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.
- Insulin degludec has a higher cost than biphasic insulin or other long acting basal insulins. The current cost for biphasic insulin is approximately between £20 and £30 per pack, or £0.38-£0.59 for 30 units and £160-£215 per year.
- For insulin glargine 100 units/ml (long acting basal insulin) the cost is £0.71 for 30 units and £252 per year, versus £0.93 for 30 units or £339 per year for insulin degludec 100 units/ml.
- 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.

Proposed sector of prescribing: Primary and secondary care

Introduction

Diabetes mellitus is a group of metabolic disorders, characterised by persistent hyperglycaemia (random plasma glucose more than 11mmol/L) with disturbances in carbohydrate, protein and fat metabolism resulting from defects in insulin secretion (leading to insulin deficiency), insulin action (leading to insulin resistance) or both.[1,2] In type 1 diabetes, patients develop an absolute insulin deficiency, however the activity of any insulin secreted remains normal. In type 2 diabetes, insulin resistance and a relative insulin deficiency result in persistent hyperglycaemia.[1,2]

Insulin degludec is a ultra-long-acting basal analogue insulin that forms soluble multi-hexamers upon subcutaneous injection. This, results in a depot reservoir from which insulin degludec is continuously and slowly absorbed into the circulation, leading to a flat and stable glucose-lowering effect.[3] It has a duration of action from 36 to beyond 42 hours with a half-life of approximately 25 hours independent of dose.[3,4]

Insulin degludec is licensed for the treatment of diabetes mellitus in adults, adolescents and children from one year of age.[3] It should be administered once daily via subcutaneous injection and can be used at any time of the day, but preferably at the same time every day. It should be dosed in accordance with the individual patient's needs.[3]

Evidence

The NICE Clinical guidance, regarding the management of type 1 diabetes in adults, last updated in March 2022, now recommends insulin degludec 100 units/ml as an alternative to twice daily insulin detemir or once daily insulin glargine 100 units/ml for patients where nocturnal hypoglycaemia is a particular concern or for people who need help from a carer or healthcare professional to administer injections.[5] In addition, NICE recommends that other basal insulin regimens can be considered if treatment goals are not being met, with the patients existing one. The following should be considered when choosing alternative insulin regimens: the person's preferences, co-morbidities, risk of hypoglycaemia and diabetic ketoacidosis, concerns around adherence and acquisition cost.[5]

Insulin degludec is not specifically mentioned in the NICE guideline on the management of diabetes in children and young people. This guidance, which was last updated in June 2022, recommends that children and young people should be offered a multiple daily injection basal-bolus insulin regimen and advises that if a child or young person with type 1 diabetes does not have optimal blood glucose levels, an alternative insulin regimen (multiple daily injections, an insulin pump, or once, twice or three-times daily mixed insulin injections), should be offered.[6]

NICE guidance regarding the management of type 2 diabetes in adults, updated in March 2022, makes no specific recommendations in relation to the use of insulin degludec.[7]

The Scottish Medicines Consortium (SMC) have approved insulin degludec for use in adults.[8] Use is not recommended in adolescents and children as the pharmaceutical company have not made a submission to the SMC for it to consider in these patient groups.[9]

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. It is not recommended for use within NHS Wales for use in adolescents and children from the age of one year.[10]

A summary of the key evidence in relation to insulin degludec 100 units/ml is provided below.

Type 1 diabetes

Insulin degludec has been directly compared with insulin glargine in four randomised trials, including a long term extension study.[11-14] In SWITCH 1, a double blind, randomised, crossover, non-inferiority

trial, 501 adults with type 1 diabetes and at least one hypoglycaemia risk factor, were randomised 1:1 to receive once daily insulin degludec for 32 weeks, followed by insulin glargine for 32 weeks (n=249) or insulin glargine 100 units/ml followed by insulin degludec (n=252).[11] 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; weeks 16-32 and 48-64. Secondary endpoints were the rate of nocturnal (severe or blood glucose confirmed between 12.01am and 5.59am), symptomatic hypoglycaemia and the proportion of patients experiencing severe hypoglycaemic 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. Similar numbers of patient discontinued in both treatment groups.[11]

The rates of overall symptomatic hypoglycaemia were lower in the insulin degludec group versus the insulin glargine 100 units/ml group; 2200.9 episodes per 100 person-years' exposure (PYE) versus 2462.7 episodes per 100 PYE (rate ratio (RR) 0.89; 95% CI 0.85-0.94). As the upper bound of the 95% CI was lower than 1.0, and the study investigators concluded that non-inferiority was confirmed ($p<0.001$) and superiority was demonstrated ($p<0.001$). 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; non-inferiority was confirmed, $p<0.001$, and superiority was demonstrated, $p<0.001$). The rate difference was -61.94 episodes per 100 PYE (95% CI -83.85 to -40.03).[11]

Two open-label, phase 3, non-inferiority trials, which were part of the BEGIN series of trials, have also compared insulin degludec 100 units/ml with insulin glargine 100 units/ml once daily in type 1 patients.[12,13] In the first trial, BEGIN Basal-Bolus Type 1, 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.[12] Insulin aspart was used at mealtimes. The primary objective was to confirm the non-inferiority of insulin degludec to insulin glargine in reduction in HbA1c from baseline after 52 weeks of treatment. 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 0.40%) were recorded in the insulin glargine and insulin degludec groups respectively ($p<0.0001$, non-inferiority was confirmed).[12] At the end of the 52 weeks, 351 patients in the insulin degludec group and 118 patients in the insulin glargine group, continued for a further 52 weeks, with 330 (94%) insulin degludec and 113 (96%) insulin glargine patients completing it.[14] The results show that after two years (104 weeks), a similar proportion of subjects in both groups reported adverse events; 87.5% (413/472) with insulin degludec and 89% (137/154) with insulin glargine. The rate of nocturnal confirmed hypoglycaemia was lower with insulin degludec at 3.9 vs. 5.3 episodes/PYE; estimated rate ratio (insulin degludec/insulin glargine) 0.75 (95%CI 0.59-0.95; $p=0.02$). The rate of overall hypoglycaemia was similar in both groups with the rate of severe hypoglycaemia classed as low (0.17 episodes/PYE insulin degludec and 0.15/PYE insulin glargine). Eight major adverse cardiovascular events were reported by eight patients in the insulin degludec group and two events by two subjects in the insulin glargine group.[14] However, definitive conclusions on comparative safety are difficult due to the difference in study group sizes as a result of the utilised randomisation ratio of 3:1.

The second trial, BEGIN: Flex T1, randomised 493 adult type 1 diabetes patients, on basal bolus therapy with an HbA1c of 10.0% or less and a body mass index of 35.0kg/m^2 or less.[13] The patients received one of three regimens - insulin degludec 100 units/ml administered on Monday, Wednesday and Friday mornings and on Tuesday, Thursday, Saturday and Sunday evenings (i.e. at fixed intervals with a minimum of eight hours and a maximum of 40 hours between degludec doses (the IDeg Forced-Flex group), n=164), or insulin degludec 100 units/ml given with the evening meal (n=165) or insulin glargine 100 units/ml administered at a fixed time each day for 26 weeks (n=165). Bolus insulin was administered as insulin aspart. At the end of the initial 26 weeks, all participants randomised to insulin degludec were

offered participation in the extension study but were asked to administer insulin degludec once daily at any time of day, provided they maintained a minimum of 8 hours and a maximum of 40 hours between doses (the IDeg Free-Flex group). Participants randomised to insulin glargine were maintained on insulin glargine in the 26-week extension.

A treat to target approach was used for optimal glycaemic target attainment and the primary endpoint was change in HbA1c from baseline after 26 weeks. Consistent with this methodology, the observed mean decrease in HbA1c from baseline to week 26 was similar in all three study groups and decreased by -0.4% in the IDeg Forced-Flex group, -0.41% and -0.58% for the insulin degludec and insulin glargine fixed time interval dosing groups respectively. The primary objective of the trial was met as IDeg Forced-Flex was shown to non-inferior to insulin glargine in reducing HBA1c.

Mean HbA1c values increased slightly across the 26 week extension but remained below the original baseline at week 52; -0.13% in the insulin degludec Free-Flex group and -0.21% in the insulin glargine group.

Overall, confirmed and severe hypoglycaemia rates were similar across all groups at week 26. No difference in overall confirmed hypoglycaemia was seen at week 52 between IDeg Free-Flex and insulin glargine. Whilst overall numbers were low, severe hypoglycaemic events were numerically lower in the insulin degludec Free-Flex group. Incidence of nocturnal hypoglycaemia was significantly lower in the insulin degludec Forced-Flex group compared to the insulin degludec (by 37%) or insulin glargine (by 40%) groups. In the extension, incidence was 27% lower with insulin degludec Free-Flex versus the insulin glargine group. Serious adverse events were reported by 5.5% of participants in the insulin degludec Forced-Flex group, 4.2% in insulin degludec and 5.0% in the insulin glargine during the first 26 weeks and by 7.6% in the insulin degludec Free-Flex group and 7.5% in the insulin glargine groups by 52 weeks.[13]

Children

In a randomised open label, parallel group, non-inferiority trial (BEGIN YOUNG 1), 350 children aged between one and 17 years with type 1 diabetes who had been receiving insulin treatment (any regimen), without oral antidiabetics drugs for at least three months and a HbA1c of ≤11%, received either insulin degludec once daily (n=174) or insulin detemir once or twice daily (n=176) for 26 weeks. Both groups received mealtime insulin aspart. After the initial 26 weeks, 280 patients entered a 26-week extension phase.[15,16] The primary endpoint was change in baseline in Hb1Ac after 26 weeks' treatment.[15] After the initial 26 weeks and following a seven day washout period, all patients received neutral protein hagedorn (NPH) insulin to ensure accurate antibody sampling, and 280 patients entered a 26-week extension phase. Secondary efficacy endpoints were assessed at regular intervals across the entire study period.

A similar change in HbA1c levels was noted in both the insulin degludec and insulin detemir study groups, with an estimated treatment different (ETD) of 0.15% (95%CI -0.03;0.32) and the study investigators reported that non-inferiority was confirmed. 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 groups, but confirmed and severe hypoglycaemia rates were numerically higher with insulin degludec, than insulin detemir (57.7 vs. 54.1 and 0.51 vs. 0.33 PYE respectively but was considered not statistically significant (NS)). Nocturnal hypoglycaemic rates were lower in the insulin degludec group vs. insulin detemir; 6.0 vs. 7.1 PYE; NS. Rates of hyperglycaemia with ketosis were lower in those treated with insulin degludec vs. insulin detemir: 0.7 vs. 1.1 PYE, treatment ratio 0.41 (95% CI 0.22; 0.78.15).

A cost utility analysis published in 2019, based on results from BEGIN YOUNG 1 included a financial analysis based on the lower rates of hyperglycaemia ketosis observed with insulin degludec and possible avoidance of hospital admissions. Overall, hypoglycaemia rates and consequently severe hypoglycaemia were excluded from the analysis as the original study had not shown any difference between the two study groups in relation to these adverse events.[16] Consequently, the overall cost effectiveness of

insulin degludec in children and young people and the additional benefit of insulin degludec in relation to overall and severe hypoglycaemia episodes remains unclear.

Type 2 diabetes

In SWITCH 2, a double blind, randomised, crossover trial, 721 adults with type 2 diabetes and at least one hypoglycaemia risk factor and who were previously treated with basal insulin, with or without oral antidiabetes medicines 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 100 units/ml 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, i.e. weeks 16-32 and 48-64. 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 100 units/ml 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 100 units/ml 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).[17]

Two phase-3, open-label trials investigated the non-inferiority of insulin degludec compared to insulin glargine 100 units/ml in patients with type 2 diabetes previously treated with and without insulin.[18,19]

In the first trial (BEGIN Basal-Bolus Type 2), 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 (n=755) or insulin glargine (n=251) 100 units/ml in a 3:1 ratio. Metformin and/or pioglitazone were permitted during the trial. The primary outcome was non-inferiority of insulin degludec to insulin glargine measured by change in HbA1c from baseline to week 52 (non-inferiority limit of 0.4%) by ANOVA in the full analysis set.[18]

At 12 months the study authors reported that non-inferiority was proven by the reduction in HbA1c level 1.1% for insulin degludec versus -1.18% for insulin glargine 100 units/ml, with a between group difference of 0.08% (95%CI -0.05 to 0.21). Rates of nocturnal hypoglycaemia were 40% vs. 47%, resulting in 0.5 fewer episodes per year per patient for insulin degludec.[18]

BEGIN Once Long was a one year multinational, open label, parallel group, treat to target, non-inferiority controlled trial, which randomised 1030 adults, (mean age 59 years) with type 2 diabetes and a HbA1c of 7-10% (mean 8.2%) on oral antidiabetic drugs, to either once daily insulin degludec (n=773) or once daily insulin glargine (n=257). Both groups received metformin and insulin which was titrated to achieve a pre-breakfast plasma glucose of 3.9-4.9 mmol/l. The primary endpoint was confirmation of non-inferiority of degludec to glargine in HbA1c reduction after 52 weeks in an intent to treat analysis. Reduction in HbA1c was similar (non-inferior) in both insulin degludec and insulin glargine groups (1.06 vs. 1.19%) with an estimated treatment difference of 0.09% (95% CI -0.04 to 0.22). Overall rates of confirmed hypoglycaemia were similar in both groups, albeit slightly lower in the insulin degludec group at 1.52 vs. 1.85 episodes/PYE. There were few episodes of nocturnal hypoglycaemia and these occurred at a lower rate in the insulin degludec group, 0.25 vs. 0.39 episodes/PYE.[19]

At the end of the 52 weeks, 551 insulin degludec and 174 insulin glargine patients entered a 12 month extension phase, with 505 and 154 patients respectively completing the full 104 weeks of the trial. The objective of the extension study was to compare the long term safety and tolerability of insulin degludec with insulin glargine for 104 weeks. At 104, weeks, reduction in Hb1Ac had decreased slightly in both groups, with an estimated treatment difference of 1mmol/mol (95% CI -1 to 3) or 0.07% (95% CI -0.07 to 0.22; p=0.339). Overall confirmed hypoglycaemia remained similar between groups at 1.72 vs. 2.05 episodes/PYE with severe hypoglycaemia rates of 0.006 vs. 0.021 episodes/PYE. The rate of nocturnal hypoglycaemia was also lower in the insulin degludec group; 0.27 vs. 0.46 episodes/PYE.[20]

The DEVOTE safety studies were commissioned after a meta-analysis of studies with insulin degludec, which suggested a possible increased risk of cardiovascular events.[21,22] The FDA delayed approval and asked the manufacturer of insulin degludec to conduct further cardiovascular safety studies (DEVOTE studies).[22]

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 100 units/ml (n=3819) once daily.[23] The primary composite outcome in the time to event analysis was the first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) with a pre-specified non-inferiority margin of 1.3. Of the patients who underwent randomization, 6509 (85.2%) had established cardiovascular disease, chronic kidney disease, or both. At baseline, the mean age was 65.0 years, the mean duration of diabetes was 16.4 years, and the mean (±SD) glycated haemoglobin level was 8.4 ± 1.7%; 83.9% of the patients were receiving insulin.

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% CI 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, insulin degludec was non-inferior to glargine 100 units/ml.[23] One or more events of severe hypoglycaemia occurred in 187 patients (4.9% in the insulin degludec group) and in 252 patients (6.6%) in the insulin glargine group with an absolute difference of 1.7 percentage points (RR 0.60; p<0.001). Rates of other adverse events did not differ significantly between the groups.[23]

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 insulin degludec group than the insulin glargine group (128 ± 56 vs. 136 ± 57mg/dl; p<0.001).[23]

Comparative studies with insulin glargine 300 units/ml (Toujeo®)

Several studies have been published recently which directly compared insulin degludec with insulin glargine 300 units/ml.[24-27]

The BRIGHT trial, was a multicentre, open label, active controlled, non-inferiority, two arm, parallel group trial, with 929 insulin naïve uncontrolled type 2 diabetes patients who were randomised to evening dosing with insulin glargine 300 units/ml (n=466) or insulin degludec 100 units/ml (n=463).

The primary endpoint was HbA1c change from baseline to week 24. At week 24, HbA1c improved to a similar degree from baseline values of 8.7% (72mmol/mol) in the insulin glargine group and 8.6% (70mmol/mol) in the insulin degludec group, to 7.0% (53mmol/mol) in both groups, with a least squares mean change from baseline of -1.64 ± 0.04% (-18.0 ± 0.4 mmol/mol) for insulin glargine and -1.59 ± 0.04% (-17.4 ± 0.4mmol/mol for insulin degludec. The mean difference between groups was -0.05% (95% CI -0.15 to 0.05) or -0.6 mmol/mol (-1.7 to 0.6). Hypoglycaemia incidence and event rates were comparable with both insulins, although the study authors reported that they were lower with insulin glargine in the initial active titration period of the trial (weeks 0-12).[24]

There is also a small amount of comparative information from the DELIVER D+ cohort study. In this retrospective, observational study, the electronic records of 1,592 type 2 diabetes patients switched from insulin glargine 100 units/ml and insulin detemir to insulin glargine 300 units/ml (n=742) or insulin degludec (n=727) were reviewed. Outcomes assessed included change in HbA1c and attainment of HbA1c goal from baseline to follow up. Hypoglycaemia outcomes were assessed using intention to treat (ITT) where events were assessed over the full six month follow up period and variable follow up (events were captured during treatment and follow up was until the earlier of treatment discontinuation or the end of the six months).

The mean decrease in HbA1c and HbA1c goal (<7.0% 53 mmol/mol and <8.0% 64 mmol/mol) attainment rates was similar in each group. The study authors observed a higher decrease in the rate

of all hypoglycaemia using the ITT method in the insulin glargine 300 units/ml group from 15.6% to 12.7%; p=0.006, and hypoglycaemia associated with inpatient/emergency department encounter from 5.3% to 3.5%; p=0.007. This was not observed with the insulin degludec group. After adjustments were made for baseline hypoglycaemia rates, no difference in hypoglycaemia incidence and event rate were observed using the ITT method. Similarly using the variable follow up method, hypoglycaemia incidence was similar in both groups and the insulin glargine 300 units/ml switchers were reported to have a lower inpatient/ED hypoglycaemia event rate at follow up. The study authors concluded the switching from insulin glargine 100 units/ml or insulin detemir to insulin glargine 300 units/ml or insulin degludec were associated with similar improvements in glycaemic control and hypoglycaemia in adult patients with type 2 diabetes.[25]

A similar retrospective, non-inferiority, multicentre analysis has also been conducted in type 1 diabetes patients. In the RESTORE-1 study, the electronic records of 2,919 patients aged over 18 years on a first generation basal insulin (glargine 100 units/ml, detemir or NPH) were reviewed for switching to a second generation basal insulin, either glargine 300 units/ml or degludec 100 units/ml. The main endpoints were changes at three months and six months in HbA1c and other measures of glycaemic control as well as incidence and rate of hypoglycaemia. The main analysis was done on two propensity score matched cohorts, each with 585 patients – one for insulin glargine 300 units/ml and one for insulin degludec. Changes in HbA1c levels from baseline were similar in both switch groups, -0.14% (95% CI -0.24% to -0.04%) in the insulin degludec group vs. -0.20% (95% CI -0.32% to -0.08%) in the insulin glargine 300 units/ml group. The incidence rate of hypoglycaemic events during a 6 month follow up was reported as slightly lower in the insulin glargine 300 units/ml group than the insulin degludec group (0.82 (95% CI 0.55 to 1.22) vs. 0.83 (95% CI 0.38 to 1.83), however the overall difference was not statistically significant.[26]

In CONCLUDE, a randomised, open label, treat to target, multinational, head to head comparator trial, 1609 participants with type 2 diabetes, aged ≥18 years with HbA1c ≤80mmol/mol (9.5%) and BMI ≤45kg/m^2 and who had previously been treated with basal insulin with or without oral glucose lowering drugs (excluding insulin secretagogues) and at risk of hypoglycaemia, received either insulin degludec 200 units/ml (n=805) or insulin glargine 300 units/ml (n=804). Both groups were titrated to a fasting blood glucose target of 4.0-5.0mmol/l. The primary endpoint was the rate of overall symptomatic hypoglycaemic events, defined as severe and requiring third party assistance or confirmed blood glucose <3.1mmol/l with symptoms during a 36-week maintenance period. Secondary endpoints included the rate of nocturnal hypoglycaemic events (severe or blood-glucose-confirmed with symptoms, occurring between 00:01 and 05:59 h), the rate of severe hypoglycaemia in the maintenance period and efficacy assessments including change from baseline in HbA1c. Endpoints were assessed during the 36-week maintenance period following treatment titration, with an overall total treatment period of 88 weeks.

Overall, there was no observed difference in the rate of overall symptomatic hypoglycaemia between the groups. The proportion of participants experiencing overall symptomatic hypoglycaemia during the maintenance period was lower for those treated with insulin degludec 200 units/ml compared with insulin glargine 300 units/ml; 40.6% versus 46.3%. Similarly, the rates of nocturnal symptomatic hypoglycaemia and severe hypoglycaemia were slightly lower in the insulin degludec group. Efficacy measurements were similar between groups.[27]

More data is required to determine the relative efficacy and safety of the ultra-long acting insulins insulin degludec and insulin glargine 300 units/ml and confirm their place in therapy.

Commissioning considerations

Insulin degludec (Tresiba®) is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of one year.[3] Insulin glargine 300 units/ml (Toujeo®), is licensed for treatment of diabetes mellitus in adults, adolescents and children from the age of six years.[28]

Insulin degludec is available as cartridges (100 units/ml) and as a pre-filled pen (Flex-Touch®) which is available in two strengths (standard strength 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.[3]

High strength insulin products have been associated with a possible increased 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 2 strengths, including risk assessment of clinical storage areas.[29,30]

All insulins should be prescribed by brand and insulin should never be removed from the cartridges or prefilled pens with syringes.[29-32]

An NHS Improvement patient safety alert, published in November 2016, has highlighted the risk of severe harm and death due to withdrawing insulin from pen devices. The strength of insulin in pen devices can vary by multiples of 100 units/ml. Insulin syringes have graduations only suitable for calculating doses of standard 100 units/ml. If insulin extracted from a pen or cartridge is of a higher strength, and that is not considered in determining the volume required, it can lead to a significant and potentially fatal overdose.[31-33]

The European Medicines Agency (EMA) have also published guidance to prevent medication errors with high strength insulins, including a series of recommendations for health care professionals.[33] 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.[33]

Insulin should never be extracted from insulin pen devices.[31,32] 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.[29-32]

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.[33] 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 100 units/ml (Lantus®) or other basal insulins to insulin degludec® or vice versa.[30,31] All patients should be closely monitored, particularly at the start of treatment and when the dose or type of insulin changes.[33] Initial and subsequent dose titration and monitoring should take place under the close supervision of a specialist team.

Although type 1 diabetes in adults is not rare, it is not common enough that all healthcare professionals who deal with it are able to acquire and maintain all the necessary skills for its management.[5]

The EoE PAC remains 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.

The use of the higher strength insulin degludec 200 units/ml is not routinely recommended.

Where deemed clinically essential it could be considered in patients receiving extremely large daily doses (≥3units/kg/day) following referral to tertiary centre for severe insulin resistance, and where a Consultant Diabetologist initiates treatment. At the time of writing, insulin resistance services are NHSE commissioned, however prescribing for medicines initiated under the service is transferred to local commissioners, (Integrated Care Boards (ICBs) formerly CCGs) after three months.[34] In May 2022, NHS England published guidance to support integration of certain specialised services within integrated care

systems. The insulin resistance services are listed as not suitable for more integrated commissioning in this roadmap.[35]

Insulin degludec 200 units/ml and insulin glargine 300 units/ml (Toujeo®) are possible treatment alternatives to Humulin R (insulin 500 units/ml or U500), in patients with extreme insulin resistance requiring very large doses. Insulin 500 units/ml is not currently licensed in the UK.[36]

Comparative costs and financial considerations

Comparative costs of all the long acting basal analogue insulins are shown in table 1.[37,38] Information regarding basic pharmacokinetics details of the different insulins has been included in appendix 1.

Insulin degludec is included in the fixed element of the National Tariff Payment System activity tariff.[39,40] Insulin degludec is more expensive than biphasic insulin or other long acting basal insulins.

Table 1 shows the cost per year based on 30 units per day. In the main 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.[11-20]

There is limited robust cost effectiveness data available with respect to insulin degludec on which to base a definitive conclusion. Two studies have been published to date which include relevant data and analysis.

A cost effectiveness evaluation, based on the clinical outcomes for insulin degludec 100 units/ml versus insulin glargine 100 units/ml in the basal bolus subgroup of the DEVOTE trial was published in 2019 and was conducted from the perspective of the National Health Service in England. Treatment with insulin degludec was associated with a mean quality adjusted life expectancy (QALE) of 6.8980 years at a mean cost of £47,311 per patient compared with 6.7825 years at a mean total cost of £45,582 per patient with insulin glargine 100 units/ml. This yielded a ICER of £14,956 per QALY gained with insulin degludec versus insulin glargine 100 units/ml, with the higher acquisition costs with insulin degludec partially offset by lower costs of non-fatal MI, severe hypoglycaemia and non-fatal stroke.[41]

A cost effectiveness analysis utilising comparative data between insulin degludec and insulin glargine 300 units/ml from the CONCLUDE study has been published based on Netherlands health system perspective and reported a mean annual cost saving of 24.71 euros per patient for insulin degludec relative to insulin glargine 300 units/ml.[42]

There is limited data available on which to base an accurate assessment of likely patient numbers who would be eligible for treatment. In 2018–2019, there were 3,919,505 people diagnosed with diabetes with 90% of currently diagnosed adults have type 2 diabetes.[2] Type 1 diabetes affects over 370,000 adults in the UK.[5] It is estimated that by 2025, more than 5 million people in the UK will be diagnosed with diabetes and more than 5.5 million people by 2030.[1]

Poorly controlled diabetes, over many years causes tissue damage which, if not detected and managed early, can result in disability: blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death. The risk of all of these complications is greatly reduced by treatment that keeps circulating glucose levels to as near normal as possible, reducing tissue damage. Disability from complications that are not avoided can often be prevented by early detection and active management.[5]

The estimated activity costs for an uncontrolled diabetic experiencing hypoglycaemic episodes resulting in at least one hospital admission per month could range from approximately £3,516 to £41,472 per year, depending on the clinical severity and overall circumstances as well as the spell duration.[39,40] There is limited data available to confirm the effect, if any, on hospital admissions or emergency attendances with either strength of insulin degludec.

Subcutaneous insulin pumps are an option for some diabetic patients; however, they do not suit everyone. The pumps cost between £2,000 and £3,000 and should last four to eight years.[43,44] There are additional annual costs in relation to consumables, such as tubing and cannula. In one UK based study

overall cost of insulin pump therapy was calculated as £1,863 more expensive per patient than multiple daily injections with no additional QALY gains.[44]

There is little to no evidence comparing subcutaneous insulin pumps and 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.

Place in therapy

The lack of robust cost effectiveness data and small differences in overall and severe hypoglycaemia rates seen between treatments make it difficult to determine a definitive place in therapy.

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, such as insulin pumps.

Table 1: Comparative costs for long acting basal analogue insulins

Prices correct as of July 2022, they are indicative only and based on 3ml cartridges for insulin pens unless otherwise stated.[37,38] Prices stated do not include cost of pen needles or pens and are calculated based on 30 units per day for ease of comparison. In clinical practice, the total number of units required will vary both between patients and also between formulations and brands. Individual dose titration is required for each diabetes patient and consequently costs will vary between patients.

Brand name	Generic name	Cost per pack	Cost per unit	Cost for 30 units	Cost per 28 days	Cost per year
Basal insulin						
Humulin®	Isophane insulin (NPH insulin)	£19.08	£0.013	£0.38	£10.68	£138.90
Insulatard®	Isophane insulin (NPH insulin)	£19.08	£0.013	£0.38	£10.68	£138.90
Insuman® Basal	Isophane insulin (NPH insulin)	£19.08	£0.013	£0.38	£10.68	£138.90
Basal – insulin analogues						
Levemir®	Insulin determir	£42.00	£0.028	£0.84	£23.52	£305.76
Lantus®	Insulin glargine 100 units/ml	£34.75	£0.023	£0.70	£19.46	£252.98
Abasaglar®	Insulin glargine – biosimilar 100 units/ml	£34.75	£0.023	£0.70	£19.46	£252.98
Semglee® (Prefilled Pen)	Insulin glargine – biosimilar 100 units/ml	£34.75	£0.023	£0.70	£19.46	£252.98
Basal – Ultra long acting insulin analogues						
Tresiba®	Insulin degludec 100 units/ml	£46.60	£0.031	£0.93	£26.10	£339.25

Brand name	Generic name	Cost per pack	Cost per unit	Cost for 30 units	Cost per 28 days	Cost per year
High strength basal Insulin						
Toujeo® (Prefilled Pen)	Insulin glargine 300 units/ml	£64.27	£0.024	£0.71	£20.02	£259.94
Tresiba® (Prefilled Pen)	Insulin degludec 200 units/ml	£55.92	£0.031	£0.93	£26.10	£339.25
Humulin® R (Prefilled Kwikpen, imported from US - unlicensed in UK)	Insulin human injection, USP				£211	
Biphasic or premixed insulins						
Humulin® M3 70/30	Insulin NPH + neutral insulin	£19.08	£0.013	£0.38	£10.68	£158.00
Humalog® Mix25 or Mix50	Insulin lispro + insulin lispro protamine	£29.46	£0.020	£0.59	£16.50	£214.47
Novomix® 30	Insulin aspart + insulin aspart protamine	£28.79	£0.019	£0.58	£16.12	£209.59
Insuman® Comb 25 or 50	Neutral insulin + isophane insulin	£17.50	£0.012	£0.35	£9.80	£127.40

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

PAC approval date	7th March 2022	Version	4
Document history	V4 revision of v3.1 following update to NG17 Type 1 diabetes in adults: diagnosis and management. No change to recommendations. V3.1 January 2018 v3 updated with clarification of wording of recommendation 2, bullet point 1. v3 Nov 2018. Commissioning recommended for specified cohorts of patients with T1D and T2D. v2.1 July 2017. Recommendations amended to remove reference to hyperosmolar hyperglycaemic state. v2 March 2018 Commissioning recommended for specified cohorts of patients with T1D only. v1 September 2013. Negative commissioning recommendation.		
Consultation process	PAC members East of England clinicians		
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP. 20th July 2022		

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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 pharmacokinetics of insulins[45]

Brand name	Generic name	Onset	Peak	Duration
Bolus insulin				
Actrapid®	Soluble or neutral insulin	<30 mins	1.5-3.5 hrs	7-8 hrs
Humulin® S	Soluble or neutral insulin	30 mins-1hr	1-6 hrs	6-12 hrs
Insuman® Rapid	Soluble orneutral insulin	<30 mins	1-4 hrs	7-9 hrs
Rapid acting- bolus insulin				
Novorapid®	Insulin aspart	10-20 mins	1-3 hrs	3-5 hrs
Humalog®	Insulin lispro	15 mins	1.5 hrs	2-5 hrs
Fiasp®	Insulin aspart	4 mins	1-3 hrs	3-5 hrs
Apidra®	Insulin glulisine	10-20 mins	55 mins	1.5-4 hrs
Basal Insulin				
Humulin® I	Isophane insulin (NPH insulin)	30 mins-1 hr	1-8 hrs	22hrs
Insulatard®	Isophane insulin (NPH insulin)	<1.5 hrs	4-12 hrs	24 hrs
Insuman® Basal	Isophane insulin (NPH insulin)	<1 hr	3-4 hrs	11-20 hrs
Basal - insulin analogues				
Levemir®	Insulin detemir	30 mins -1hr	-	24 hrs
Lantus®	Insulin glargine 100 units/ml	1-4hrs	-	24 hrs
Abasaglar®	Insulin glargine - biosimilar 100 units/ml	1-4hrs	-	24 hrs
Semglee®	Insulin glargine - biosimilar 100 units/ml	1-4 hrs	-	24 hrs
Basal - Ultra long acting insulin analogues				
Tresiba®	Insulin degludec 100 units/ml	1-2 hrs	-	>42 hrs
High Strength basal insulin				
Toujeo®	Insulin glargine 300 units/ml	1-6 hrs	-	24-36 hrs

Brand name	Generic name	Onset	Peak	Duration
Tresiba®	Insulin degludec 200 units/ml	1-2 hrs	-	>42 hrs
Humulin® R (imported from US - unlicensed in UK)	Insulin human injection, USP	30-45 mins	4-8 hrs	12-24 hrs
Biphasic or premixed insulins				
Humulin® M3 70/30	NPH + neutral insulins	30 mins -1hr	1-12 hrs	22 hrs
Humalog® Mix	Lispro + lispro protamine insulins	15 mins	2 hrs	22 hrs
Novomix®	Aspart + aspart protamine insulins	10-20 mins	1-4 hrs	24 hrs
Insuman® Comb	Neutral + isophane insulins	30 mins -1hr	2-4 hrs	11-20 hrs

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 children with type 1 or type 2 diabetes.

Updated NICE Guidance regarding the management of type 1 diabetes in adults recommends insulin degludec 100 units/ml as an alternative to twice daily insulin detemir or once daily insulin glargine 100 units/ml, for patients where nocturnal hypoglycaemia is a particular concern or for people who need help from a carer or healthcare professional to administer injections.

In addition, the EOE PAC considers that insulin degludec 100 units/ml may also be of benefit in certain patients with type 1 or type 2 diabetes who fulfil the following criteria and where insulin detemir and insulin glargine have been tried or are not clinically suitable:

- 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 hyperglycaemic hyperosmolar non–ketotic diabetic coma or 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

In SWITCH 1, 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 for 32 weeks, followed by insulin glargine (n=249) for 32 weeks or insulin glargine 100 units/ml followed by insulin degludec (n=252). 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; weeks 16-32 and 48-64. During the maintenance period, the rates of overall symptomatic hypoglycaemia were lower in the insulin degludec group versus the insulin glargine 100 units/ml group; 2200.9 episodes per 100 person-years' exposure (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 (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 one hypoglycaemia risk factor and who were previously treated with basal insulin, with or without oral antidiabetes medicines 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 100 units/ml 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, (weeks 16-32 and 48-64) the rates of overall symptomatic hypoglycaemia for insulin degludec vs. insulin glargine 100 units/ml 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 100 units/ml 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).

Cost effectiveness

There is limited robust cost effectiveness data available with respect to insulin degludec on which to base a definitive conclusion. Two studies have been published, to date which include relevant data and analysis. A cost effectiveness evaluation, based on the clinical outcomes for insulin degludec 100 units/ml versus insulin glargine 100 units/ml in the basal bolus subgroup of the DEVOTE trial was conducted from the perspective of the National Health Service in England and published in 2019. Treatment with insulin degludec was associated with a mean quality adjusted life expectancy (QALE) of 6.8980 years at a mean cost of £47,311 per patient compared with 6.7825 years at a mean total cost of £45,582 per patient with insulin glargine 100 units/ml. This yielded a ICER of £14,956 per QALY gained with insulin degludec versus insulin glargine 100 units/ml, with the higher acquisition costs with insulin degludec partially offset by lower costs of non-fatal MI, severe hypoglycaemia and non-fatal stroke.

A cost effectiveness analysis utilising comparative data between insulin degludec and insulin glargine

300 units/ml from the CONCLUDE study has been published from the Netherlands health system perspective and reported a mean annual cost saving of 24.71 euros per patient for insulin degludec relative to glargine 300 units/ml.

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.

The estimated activity costs for an uncontrolled diabetic experiencing hypoglycaemic episodes resulting in at least one hospital admission per month could range from approximately £3,516 to is £41,472 approximately £18,000 per year, depending on the clinical severity and overall circumstances as well as the spell duration. There is limited data available to confirm the effect if any on hospital admissions or emergency attendances with either strength of insulin degludec.

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 300 units/ml, 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 (incorporates patient choice and exceptional need

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 300 units/ml®.

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

Policy drivers

NICE Guidance

Safety issues with high strength insulins need to be carefully considered.

Disinvestment

Insulin degludec 200 units/ml and insulin glargine 300 units/ml (Toujeo®) are possible treatment alternatives to Humulin R (insulin 500 units/ml or U500), in patients with extreme insulin resistance requiring very large doses. Insulin 500 units/ml is not currently licensed in the UK and only available via importation from the United States at significantly higher cost than insulin degludec or insulin glargine 300 units/ml.