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

Insulin glargine 300 units/ml (Toujeo®)

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 glargine 300 units/ml (Toujeo®) is not recommended for routine use in either type 1 or type 2 diabetes in primary and secondary care due to patient safety concerns with the use of high strength insulins. It may be considered for specialist initiation only in patients described under point 2 below.
2. The place in therapy of insulin glargine 300 units/ml in relation to other basal insulins remains to be fully determined. Insulin glargine 300 units/ml may be of benefit in adult patients, over the age of 18 years, 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.
    - 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 detemir or insulin degludec.
    - Patients with severe insulin resistance requiring large daily doses of insulin (≥3 units/kg/day) could be considered for insulin glargine 300 units/ml.
3. In all the above situations, insulin glargine 300 units/ml (Toujeo®) should be initiated by Specialist Diabetes Teams 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.
4. 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.
5. 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 glargine 300 units/ml (Toujeo®) to ensure that the treatment is continuing to meet the specific needs of the local population.

6. 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 glargine 300 units/ml (Toujeo®)

PAC recommendations

1. Insulin glargine 300 units/ml (Toujeo®) is not recommended for routine use in either type 1 or type 2 diabetes in primary and secondary care due to patient safety concerns with the use of high strength insulins. It may considered for specialist initiation only in patients described under point 3 below.
2. CCGs/ICBs and Area Prescribing Committees are advised to consider place in therapy and safety and implementation issues locally, with respect to formulary positioning and suitability for prescribing in primary care.
3. The place in therapy of insulin glargine 300 units/ml in relation to other basal insulins remains to be fully determined. Insulin glargine 300 units/ml may be of benefit in adult patients, over the age of 18 years, 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 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 detemir or insulin degludec.
4. Insulin glargine 300 units/ml (Toujeo®) could 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.

Where approved for use

5. Prior 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 glargine 300 units/ml (Toujeo®) to ensure that the treatment is continuing to meet the specific needs of the local population.

PAC recommendations

6. Insulin glargine 300 units/ml (Toujeo®) should be initiated by 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 their 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.
8. These recommendations will be reviewed in the light of new evidence on clinical, cost effectiveness and safety.

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 glargine 300 units/ml (Toujeo®) is a novel formulation of insulin glargine which has a pharmacokinetic profile broadly similar to insulin degludec. Insulin glargine 300 units/ml is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of six years. Insulin degludec is licensed from the age of one year. Insulin glargine 300 units/ml has been shown to be non-inferior to insulin glargine 100 units/ml. There are no superiority trials.
- Data from the EDITION 4 study in type 1 diabetics suggests that insulin glargine 300 units/ml is non-inferior to insulin glargine 100 units/ml in terms of overall diabetes control. Rates of hypoglycaemia did not differ between groups. More data is required to quantify the effect, if any, on nocturnal hypoglycemic episodes in type 1 patients.
- Three randomized controlled trials have studied the efficacy and safety in type 2 diabetes patients; EDITION 1, EDITION 2, and EDITION 3. The percentage of participants experiencing at least one confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6 was lower with insulin glargine 300 units/ml compared with insulin glargine 100 units/ml: 36% vs. 46% (relative risk (RR) 0.79; 95% confidence interval (CI) 0.67 to 0.93, p=0.0045) in EDITION 1; 22% vs. 28% (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) in EDITION 2 and 16% vs. 17% (RR 0.89; 95% CI 0.66 to 1.20) in EDITION 3. This was statistically significant in EDITION 1 and EDITION 2 but not in EDITION 3.
- 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 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 appears to be no evidence to confirm that insulin glargine 300 units/ml is associated with a reduction in hospital admissions for diabetes related complications or the effect, if any, on macrovascular or microvascular outcomes.

- There is limited comparative evidence with other insulins or with continuous subcutaneous insulin pumps.
- Insulin glargine 300 units/ml is a higher strength formulation than the usual strength for insulin glargine products (100 units/ml). These units are exclusive to insulin glargine 300 units/ml and are not the same as units used to express the potency of other insulin analogues.
- Insulin glargine 300 units/ml is not bioequivalent to insulin glargine 100 units/ml (Lantus®) and not directly interchangeable with other insulin glargine products, insulin degludec (Tresiba®) or other insulins.
- Insulin glargine 300 units/ml is classified as a high strength insulin. High strength insulins have been associated with an increased risk of medication errors, due to the wrong product being supplied. A MHRA Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths.
- Whilst insulin glargine is included as a recommended option in the NICE Clinical Guideline for type 2 diabetes, insulin glargine 300 units/ml (Toujeo®) was not specifically evaluated in the associated evidence review.
- The Scottish Medicines Consortium (SMC) has accepted the use of insulin glargine 300 units/ml in restricted categories of patients only.
- Insulin glargine 300 units/ml is equivalent in cost to insulin glargine 100 units/ml (Lantus®) preparations.
- Insulin glargine 300 units/ml may be useful in patients who would otherwise require a large dose volume or multiple injections to obtain their required dose (i.e. patients requiring <3 injections per day of basal insulin), who will adhere to once daily injections because of reduced injection volumes.
- The Priorities Advisory Committee acknowledge the safety concerns around the use of high strength insulins and recommend that CCGs/ICBs and Area Prescribing Committees consider place in therapy, safety and implementation issues locally, with respect to formulary positioning and suitability for prescribing in primary 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 glargine is a human insulin analogue which has a low solubility at neutral pH but is completely soluble at the acidic pH of the injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released. This provides a prolonged duration of action, without a pronounced peak.[3-5]

Insulin glargine is available as the standard strength formulation, 100 units/ml (100 units/ml Lantus®), or as the recently launched more concentrated formulation; insulin glargine 300 units/ml (U300; Toujeo®),[3,4] which has a more stable or flatter profile, with a more predictable inter and intra patient response and a prolonged duration of action (up to 36 hours).[4,6]

Evidence

NICE clinical guidance regarding the management of type 1 diabetes in adults and last updated in June 2022, advises that multiple daily injection basal-bolus insulin regimens should be offered for all adults with type 1 diabetes. Twice daily insulin detemir is recommended as the basal insulin therapy of choice. Once daily insulin glargine 100 units/ml is cited as the preferred alternative if insulin determir is not tolerated. Insulin degludec 100 units/ml is recommended as an alternative for patients where nocturnal hypoglycaemia is a particular concern or for people who need help from a carer or healthcare professional to administer injections.[7] In addition, NICE also 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.[7] Insulin glargine 300 units/ml is not specifically mentioned in the guidance.

In relation to type 2 diabetes, NICE guidance originally published in December 2015 and last updated in June 2022, recommends insulin glargine as an alternative to NPH insulin and insulin detemir. This guidance does not specifically confirm the strength of insulin glargine and the associated evidence review did not include any assessment of the 300 units/ml formulation.[8]

Neither strength of insulin glargine is specifically mentioned in the NICE clinical guidance regarding the management of diabetes in children and young people. This guidance, 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.[9]

Insulin glargine 300 units/ml has been accepted by the SMC for restricted use within Scotland in the following situations:

- Patients with type 1 diabetes who are at risk of or experience unacceptable frequency and/or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with established insulins.
- Patients who require a carer to administer their medication on a once daily basis.
- Patients with type 2 diabetes who suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.[10]

The efficacy and safety of insulin glargine 300 units/ml has been assessed in four randomised controlled clinical trials, EDITION 1, 2, 3 and 4.[11-18]

Type 1 diabetes

In EDITION 4, a phase 3a, multicentre, randomised, four-arm, parallel-group, non-inferiority trial, 549 adult patients with type 1 diabetes received either insulin glargine 300 units/ml or insulin glargine 100 units/ml once-daily injected morning or evening.[12] The primary end-point was the overall change in HbA1c from baseline to month 6.

The study results suggest that insulin glargine 300 units/ml was non-inferior to once-daily insulin glargine 100 units/ml. A similar reduction in HbA1c from baseline to month 6 was seen in both treatment groups, with a difference between groups of 0.04% (0.4 mmol/mol); 95% CI −0.10 to 0.19% (−1.1 to 2.1 mmol/mol). This was below the pre-specified non-inferiority margin of 0.4%. A similar proportion of patients in each treatment group achieved HbA1c below 7.0% (53mmol/mol) at month 6; 16.8% with insulin glargine 300 units/ml and 15.0% with insulin glargine 100 units/ml respectively.[12]

Rates of hypoglycaemia did not differ between treatment groups at 6 months. In the insulin glargine 300 units/ml group, 93.1% of participants had one or more confirmed or severe hypoglycaemic events over 6 months compared with 93.5% in the insulin glargine 100 units/ml group; (RR 1.00; 95% CI 0.95

to 1.04).[12] Nocturnal hypoglycaemic events occurred in 68.6% of the insulin glargine 300 units/ml group and 70.2% of the insulin glargine 100 units/ml group (RR 0.98; 95% CI 0.88 to 1.09), and severe hypoglycaemic events occurred in 6.6% of the insulin glargine 300 units/ml group and 9.5% of the insulin glargine 100 units/ml group (RR 0.71; 95% CI 0.41 to 1.24). At 6 months, the basal insulin dose was approximately 18% higher with insulin glargine 300 units/ml (0.47 units/kg/day) than with insulin glargine 100 units/ml (0.40 units/kg/day).[12]

Type 2 diabetes

There are three main phase 3, randomised non-inferiority studies, which compared insulin glargine 300 units/ml with insulin glargine 100 units/ml, in adults with type 2 diabetes over 26 weeks:[13-18]

- EDITION 1: involved 807 adults using basal and mealtime insulin[13,14]
- EDITION 2: involved 811 adults who were also using oral blood glucose lowering drugs and basal insulin[15,16]
- EDITION 3: involved 878 insulin naïve adults who were taking oral blood glucose lowering drugs.[17]

The objective of all three trials was to demonstrate that insulin glargine 300 units/ml was non-inferior to insulin glargine 100 units/ml in terms of HbA1c reduction from baseline to month 6.

No difference in HbA1c reduction was reported between groups in EDITION 1; (95% CI −0.11 to 0.11%, −1.2 to 1.2mmol/mol).[13,14]

Treatment differences of −0.01% (0.1 mmol/mol, 95% CI −0.14 to 0.12%, −1.5 to 1.3 mmol/mol) and 0.04% (0.4mmol/mol, 95% CI −0.09 to 0.17%, −1.0 to 1.9 mmol/mol) between groups were reported in EDITION 2 and EDITION 3 respectively. These differences were all below the pre-specified non-inferiority margin of 0.4%. A similar proportion of participants in both treatment groups in each trial also achieved HbA1c below 7.0%, (53 mmol/mol) at month 6.[15-17]

The percentage of participants experiencing at least one confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6 (secondary endpoint) was lower with insulin glargine 300 units/ml compared with insulin glargine 100 units/ml in the three trials: with 36% vs. 46% (RR 0.79; 95% CI 0.67 to 0.93, p=0.0045) reported in EDITION 1,[14] 22% vs. 28% (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) in EDITION 2[15] and 16% vs. 17% (RR 0.89; 95% CI 0.66 to 1.20) in EDITION 3.[17] The study authors cited that the results were statistically significant in EDITION 1 and EDITION 2 but not in EDITION 3.[14,15,17]

The mean basal insulin dose was approximately 12% higher with insulin glargine 300 units/ml than with insulin glargine 100 units/ml. The mean basal insulin dose at month 6 was reported as 0.85 units/kg/day with insulin glargine 300 units/ml and 0.76 units/kg/day with insulin glargine 100 units/ml.[18] The dose of insulin glargine 300 units/ml was 10% higher in EDITION 1 and EDITION 2, and 17% higher in EDITION 3.[13,15,17] The authors concluded that a similar reduction in HbA1c was seen from baseline to month 6 and that non-inferiority was demonstrated between the two products.[13,15,17]

Severe nocturnal hypoglycaemic events were reported as rare in all three RCTs, however there were too few for a meaningful analysis to be completed in each trial.[13,15-17]

Severe hypoglycaemic events at any time of day were reported as rare and not statistically significantly different between groups; the percentage of participants experiencing at least one severe event at any time of day was 2.3% in the insulin glargine 300 units/ml group and 2.6% in the insulin glargine 100 units/ml group (RR 0.85, 95% CI 0.52 to 1.39).[13,15-17]

In a post-hoc meta-analysis of the three RCTs, the annualised rate of confirmed or severe nocturnal events over the 6-month study period was 31% lower with insulin glargine 300 units/ml compared with insulin glargine 100 units/ml (2.10 events per participant-year with insulin glargine 300 units/ml versus 3.06 events per participant-year with insulin glargine 100 units/ml; RR 0.69, 95% CI 0.57 to 0.84, p=0.0002).[18] This is a reduction of approximately one confirmed or severe nocturnal event per person per year. The clinical significance of this is unclear.

There is some limited direct comparative evidence with insulin degludec or other basal insulins. A network meta-analysis published in 2016 aimed to compare the efficacy and safety of insulin glargine 300 units/ml with other basal insulin therapies in patients with type 2 diabetes mellitus, based on changes in HbA1c (%) and body weight, and rates of nocturnal and documented symptomatic hypoglycaemia. 41 studies were included, with 25 of these studies comprising the main analysis population of patients on basal insulin-supported oral therapy. The analysis reported that the change in glycated haemoglobin (HbA1c) was comparable between insulin glargine 300 units/ml and insulin detemir (difference −0.08; −0.40 to 0.24), neutral protamine Hagedorn insulin (NPH 0.01; −0.28 to 0.32), insulin degludec (−0.12; −0.42 to 0.20) and premixed insulin (0.26; −0.04 to 0.58). Change in body weight was comparable between insulin glargine 300 units/ml and insulin detemir (0.69; −0.31 to 1.71), NPH insulin (−0.76; −1.75 to 0.21) and insulin degludec (−0.63; −1.63 to 0.35), but lower compared with premixed insulin (−1.83; −2.85 to−0.75). Insulin glargine 300 units/ml was associated with a lower nocturnal hypoglycaemia rate versus NPH insulin (risk ratio 0.18; 0.05 to 0.55) and premixed insulin (0.36; 0.14 to 0.94). No significant differences were noted between insulin glargine 300 units/ml versus insulin detemir (0.52; 0.19 to 1.36) and insulin degludec (0.66; 0.28 to 1.50). Differences in documented symptomatic hypoglycaemia rates of insulin glargine 300 units/ml versus insulin detemir (0.63; 0.19 to 2.00), NPH insulin (0.66; 0.27 to 1.49) and insulin degludec (0.55; 0.23 to 1.34) were not significant. The analysis authors concluded that insulin glargine 300 units/ml is also associated with a significantly lower risk of nocturnal hypoglycaemia compared with NPH insulin and premixed insulin, with glycaemic control comparable to available basal insulin comparators.[19]

Comparative evidence with insulin degludec

In the BRIGHT trial, a multicentre, open label, active controlled, two arm, parallel group, non-inferiority trial, 929 insulin naïve uncontrolled type 2 diabetes patients 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 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 -0.6mmol/mol (-1.7 to 0.6). Hypoglycaemia incidence and event rates were comparable with both insulins, but reported to be lower with insulin glargine in the initial active titration period of the trial (weeks 0-12).[20]

In CONCLUDE, a randomised, open label, treat to target, multinational, head to head comparator trial, 1,609 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 4.0-5.0 mmol/l. The primary endpoint was the rate of overall symptomatic hypoglycaemia 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 a 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 periods was lower for those treated with insulin degludec 200 units/ml compared with insulin glargine 300 units/mml; 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.[21]

There is also a small amount of comparative information from the DELIVER D+ cohort study, part of the DELIVER programme. The DELIVER programme was a series of studies funded by Sanofi undertaken to assess clinical outcomes and healthcare-resource utilization (HCRU) using electronic healthcare records (EHRs) of people with type 2 diabetes who received either insulin glargine 300 units/ml or other basal insulin analogues in real-world clinical settings in the United States, the results of which have been reported in eight separate publications.[22-24]

In DELIVER D+, a retrospective, observational, cohort 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 the intention to treat (ITT) population where events were assessed over the full 6 month follow up period, or variable follow up (events were captured during treatment and follow up was until the earlier of treatment discontinuation or the end of the 6 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; 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 alternative 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.[22]

DELIVER High Risk was a retrospective, observational, cohort study which compared 12-month clinical effectiveness of insulin glargine 300 units/ml versus insulin glargine 100 units/ml or insulin detemir in patients with type 2 diabetes who were at high risk of hypoglycaemia. 2,550 patients with type 2 diabetes who switched from insulin glargine 100 units/ml or insulin detemir to insulin glargine 300 units/ml were propensity score matched to 2,550 patients who switched from insulin glargine 300 units/ml to insulin glargine 100 units/ml or insulin detemir. Outcomes were change in HbA1c, attainment of HbA1c goals (<7% and <8%), and incidence and event rates of hypoglycaemia (all-hypoglycaemia and hypoglycaemia associated with an inpatient/emergency department [ED] contact). HbA1c reductions were similar following switching to insulin glargine 300 units/ml or insulin glargine 100 units/ml/insulin detemir: -0.51% vs. -0.53; p=0.67. Patients in both cohorts had comparable all hypoglycaemia incidence and event rates, however the cohort who switched to insulin glargine 300 units/ml had a lower risk of inpatient/ED associated hypoglycaemia.[23]

The DELIVER 3 study was a retrospective, observational, cohort study of electronic medical records which compared insulin glargine 300 units/ml and insulin glargine 100 units/ml/insulin detemir on glycaemic control and hypoglycaemia risk in adults with type 2 diabetes aged ≥65 years. 1,176 patients who switched from insulin glargine 100 units/ml/insulin detemir to insulin glargine 300 units/ml were propensity score matched to 1,176 patients who switched from insulin glargine 300 units/ml to insulin glargine 100 units/ml/insulin detemir. Outcomes were follow-up HbA1c, achievement of HbA1c <7% and <8%, hypoglycaemia incidence and event rates, and healthcare resource utilization. The results show that switching to insulin glargine 300 units/ml versus insulin glargine 100 units/ml/insulin detemir was associated with greater/similar reductions in HbA1c (variable follow-up: −0.45% ± 1.40% vs. −0.29% ± 1.57%; p=0.021; fixed follow-up: −0.48% ± 1.49% vs. −0.38% ± 1.59%; p=0.114), while HbA1c goal attainment was similar in both cohorts. The results also show a possible decreased risk of hypoglycaemia for patients switched to insulin glargine 300 units/ml, and an overall hypoglycaemia event rate per patient year of 0.12 for the insulin glargine 300 units/ml group and 0.27 for the insulin detemir/insulin glargine 100 units/ml group, with an adjusted rate ratio of 0.43 (0.31-0.60; p<0.01).[24]

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 (insulin glargine 100 units/ml, insluin detemir or NPH) were reviewed for switching to a second generation basal insulin, either insulin glargine 300 units/ml or insulin 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 and non-inferiority was confirmed. 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.[25]

More data is required on which to base a definitive conclusion.

Adverse events

The most frequent adverse events observed with insulin glargine 300 units/ml from the main clinical trials were nasopharyngitis (8.2% vs. 6.8% with insulin glargine 100 units/ml (Lantus®)) and upper respiratory tract infection (6.5% vs. 5.8%). Most of the adverse events were mild to moderate in intensity. Overall, serious adverse events were reported by 5.4% of people in both the insulin glargine 300 units/ml and insulin glargine 100 units/ml groups; most commonly hypoglycaemia in people with type 1 diabetes.[6]

No clinical trials have been conducted to establish the cardiovascular safety of insulin glargine 300 units/ml. It is uncertain if the cardiovascular safety outcomes in the Origin study, with insulin glargine 100 units/ml can be applied to insulin glargine 300 units/ml.[6,26]

Commissioning considerations

Insulin glargine 300 units/ml (Toujeo®) is licensed for the management of diabetes mellitus in adults, adolescents and children from the age of six years.[4] Insulin degludec (Tresiba®) is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of one year.[27]

Insulin glargine 300 units/ml is indicated for once-daily subcutaneous administration at the same time each day.[4] When necessary, insulin glargine 300 units/ml may be administered up to three hours before or after the usual time of administration.[4] In patients with type 1 diabetes, insulin glargine 300 units/ml must be used in combination with a short- or rapid-acting insulin to cover mealtime insulin requirements.[4] Insulin glargine 300 units/ml can be administered in combination with other glucose-lowering medications in patients with type 2 diabetes.[4]

Insulin glargine 300 units/ml is a higher strength formulation than the usual strength for insulin glargine products (100 units/ml).[3,4,28] These units are exclusive to insulin glargine 300 units/ml and are not the same as units used to express the potency of other insulin analogues.[3,4,28] Consequently, insulin glargine 300 units/ml is not bioequivalent to insulin glargine 100 units/ml (Lantus®) and not directly interchangeable with other insulin glargine products, insulin degludec (Tresiba®) or other insulins. The European Medicines Agency advises that when switching patients from standard-strength insulin to an insulin formulation that is not bioequivalent (such as insulin glargine 300 units/ml), switching can be done on a unit to unit basis, but the dose may need to be adjusted to achieve target plasma glucose level ranges.[28]

High strength insulin products have been associated with a possible increase risk of medication errors.[29] The strength of the insulin should always be included on the prescription. A Medicines and Healthcare Regulatory Agency (MHRA) Drug Safety Update, regarding an alternative high strength insulin, insulin degludec, has been issued with advice for healthcare professionals to minimise risk of errors, including

risk assessment of clinical storage areas.[30,31] 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. All patients should be closely monitored, particularly at the start of treatment. Initial dose titration and monitoring should take place under the close supervision of a specialist team.[31,32] Community pharmacies and dispensing practices are reminded to check with the patient the brand and formulation which they are expecting at the point of supply.[31,32] Provider trusts and community trusts are advised to consider the practicalities of storage for these insulins to further minimise the potential for dispensing and medication supply errors.

All insulins should be prescribed by brand and insulin should never be removed from the cartridges or prefilled pens with syringes.[31] Insulin glargine 300 units/ml is supplied in a prefilled pen device.[4]

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.[32]

Comparative costs and financial considerations

Comparative costs of all long acting basal analogue insulins are shown in table 1. The prices are correct as of July 2022, they are indicative only and are based on 3ml cartridges for insulin pens unless otherwise stated.[33,34] Prices stated do not include cost of pen needles or pens. Costs 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.

Table 1: Comparative costs for long acting basal analogue insulins

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)	£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 detemir	£42.00	£0.028	£0.84	£23.52	£305.76
Lantus®	Insulin glargine U100	£34.75	£0.023	£0.70	£19.46	£252.98
Abasaglar®	Insulin glargine - biosimilar U100	£34.75	£0.023	£0.70	£19.46	£252.98
Semglee® (Prefilled Pen)	Insulin glargine - biosimilar U100	£34.75	£0.023	£0.70	£19.46	£252.98
Basal - Ultra long acting insulin analogues						
Tresiba®	Insulin degludec U100	£46.60	£0.031	£0.93	£26.10	£339.25

Basal - High strength ultra long acting insulin analogues						
Toujeo® (Prefilled Pen)	Insulin glargine U300	£64.27	£0.024	£0.71	£20.00	£259.949
Tresiba® (Prefilled Pen)	Insulin degludec U200	£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

In 2018–2019, there were 3,919,505 people diagnosed with diabetes, and 90% of currently diagnosed adults have type 2 diabetes.[2] Type 1 diabetes affects over 370,000 adults in the UK.[7] 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]

There is limited data available on which to base an accurate assessment of likely patient numbers who would be eligible for treatment. Insulin glargine 100 units/ml and 300 units/ml are included in the fixed element of the National Tariff Payment System activity tariff.[35,36] 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.[35,36]

There is limited data available to confirm the effect if any on hospital admissions or emergency attendances with either strength of insulin glargine.

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 4 to 8 years.[37,38] However, 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.[38]

There appears to be little to no evidence comparing subcutaneous insulin pumps and insulin 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 glargine 300 units/ml and subsequently did not require pump therapy or if the number of repeat admissions for diabetic ketoacidosis in patients treated with insulin glargine 300 units/ml would be reduced as this has not been studied.

There appears to be no cost effectiveness data based on the United Kingdom National Health Service perspective for insulin glargine 300 units/ml.

A cost effectiveness study has been published utilising data comparing insulin degludec with insulin glargine 100 units/ml from the perspective of the NHS in England.[39] 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 glargine 100 units/ml. This yielded a ICER of £14,956 per QALY gained with insulin degludec versus insulin glargine 100 units/ml. The higher acquisition costs with insulin degludec were partially offset by lower costs of non-fatal MI, severe hypoglycaemia and non-fatal stroke.[39]

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.[40]

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 insulin glargine 300 units/ml.

The place in therapy of insulin glargine 300 units/ml in relation to other basal insulins remains to be fully determined.

Insulin glargine 300 units/ml may offer few or no meaningful advantages for the majority of potential users, but could considered for similar groups of adult patients, to those defined for insulin degludec.

The use of the higher strength insulins, such as insulin glargine 300 units/ml are not routinely recommended.

Where deemed clinically essential, insulin glargine 300 units/ml could be considered in patients receiving large daily doses of standard insulins (≥3 units/kg/day), following referral to tertiary centre for severe insulin resistance, where treatment is initiated by a Consultant Diabetologist.[41,42]

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 (Humulin® R) 500 units/ml is not currently licensed in the UK, but available as a imported product from the United States.

Insulin resistant diabetes services are currently commissioned by NHS England, however prescribing for medicines initiated under the service is transferred to local commissioners, Integrated Care Boards (ICBs), formerly CCGs, after three months.[42] 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.[43]

ICBs and associated Area Prescribing Committees (APCs) are advised to consider place in therapy and safety and implementation issues locally, with respect to formulary positioning and suitability for prescribing in primary care.

Author: Vicky Gibson on behalf of East of England Priorities Advisory Committee

Document history

PAC approval date	7th March 2022	**Version**	v2
Consultation process	PAC members EoE clinicians		
Document history	V2 revision of v1.2 following update to NG17 Type 1 diabetes in adults: diagnosis and management. No change to recommendations. v1.2 Nov 2018 Updated to clarify wording of recommendation 3, bullet point 1 V1 January 2018		
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP. 20th July 2022		
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, Toujeo, alone and in combination.		

*Consult Summary of Prescribing Characteristics for full prescribing details and up to date guidance in relation to dosing and prescribing recommendations

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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Appendix 1. Comparative pharmacokinetics of insulins[44]

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 or neutral 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 -1hr	1-8 hrs	22 hrs
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	1-4 hrs	-	24 hrs
Abasaglar®	Insulin glargine - biosimilar 100 units/ml	1-4 hrs	-	24 hrs
Semglee®	Insulin glargine - biosimilar U100	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 (Concentrated)				
Toujeo®	Insulin glargine 300 units/ml	1-6 hrs	-	24-36 hrs
Tresiba®	Insulin degludec U200	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	Insulin NPH + neutral insulin	30 mins-1hr	1-12 hrs	22 hrs

Brand name	Generic name	Onset	Peak	Duration
Humalog® Mix	Insulin lispro + insulin lispro protamine	15 min	2 hrs	22 hrs
Novomix®	Insulin aspart + insulin aspart protamine	10-20 mins	1-4 hrs	24 hrs
Insuman® Comb	Neutral insulin + isophane insulin	30 mins-1hr	2-4 hrs	11-20 hrs

Appendix 2: Assessment against ethical and commissioning principles

Treatment assessed

Insulin glargine 300 units/ml (Toujeo®)

East of England Priorities Advisory Committee Recommendation

Insulin glargine 300 units/ml (Toujeo®) is **not recommended** for routine use in either type 1 or type 2 diabetes due to patient safety concerns with the use of high strength insulins. It may considered for specialist initiation only in patients described below.

Integrated Care Boards (ICBs)s and associated Area Prescribing Committees (APCs) are advised to consider place in therapy and safety and implementation issues locally, with respect to formulary positioning and suitability for prescribing in primary care.

The place in therapy of insulin glargine 300 units/ml in relation to other basal insulins remains to be fully determined.

Insulin glargine 300 units/ml may be of benefit in adult patients, over the age of 18 years, 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 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 detemir or insulin degludec.

Insulin glargine 300 units/ml (Toujeo®) could also 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.

Where approved for use:

Prior 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 glargine 300 units/ml (Toujeo®) to ensure that the treatment is continuing to meet the specific needs of the local population.

Insulin glargine 300 units/ml (Toujeo®) should be initiated by a consultant Diabetologist 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 their 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 glargine 300 units/ml have been shown to be non-inferior to insulin glargine 100 units/ml in four randomised controlled clinical trials - EDITION 1, 2, 3 and 4. There are no superiority trials.

In EDITION-4, a phase-3a, multicentre, randomised, four-arm, parallel-group, non-inferiority trial, 549 adult patients with type 1 diabetes received either insulin glargine 300 units/ml or insulin glargine 100 units/ml once-daily. The primary end point was the overall change in HbA1c from baseline to month 6. The study results suggest that glargine 300 units/ml was non-inferior to once-daily glargine 100 units/ml. A similar reduction in HbA1c from baseline to month 6 was seen in both treatment groups, with a difference between groups of 0.04% (0.4 mmol/mol); [95% CI −0.10 to 0.19% (−1.1 to 2.1 mmol/mol)]. This was below the pre-specified non-inferiority margin of 0.4%. A similar proportion of patients in each treatment group achieved HbA1c below 7.0% (53mmol/mol) at month 6; 16.8% with insulin glargine 300 units/ml and 15.0% with insulin glargine 100 units/ml respectively. Rates of hypoglycaemia did not differ between treatment groups at 6 months.

Three main phase-3, randomised non-inferiority studies compared insulin glargine 300 units/ml with insulin glargine 100 units/ml in adults with type 2 diabetes over 26 weeks; EDITION 1 (n =807), EDITION 2 (n=811) and EDITION 3 (n=878) with the objective to demonstrate that insulin glargine 300 units/ml was non-inferior to insulin glargine 100 units/ml in terms of HbA1c reduction.

No difference was reported between groups in EDITION 1; (95% CI −0.11% to 0.11%, −1.2 to 1.2mmol/mol). A between group treatment difference of −0.01% [0.1 mmol/mol, 95% CI −0.14 to 0.12%, −1.5 to 1.3 mmol/mol] and -0.04% [0.4mmol/mol, 95% CI −0.09 to 0.17%, −1.0 to 1.9 mmol/mol], was reported in EDITION 2 and EDITION 3 respectively. These differences were all below the pre-specified non-inferiority margin of 0.4%. At month 6, similar proportions of participants in both treatment groups in each trial also achieved HbA1c below 7.0% (53 mmol/mol).

The percentage of participants experiencing at least one confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6 (secondary endpoint) was lower with insulin glargine 300 units/ml compared with insulin glargine 100 units/ml: 36% vs. 46% (relative risk [RR] 0.79; 95% CI 0.67 to 0.93, p=0.0045) in EDITION 1; 22% vs. 28% (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) in EDITION 2 and 16% vs. 17% (RR 0.89; 95% CI 0.66 to 1.20) in EDITION 3. This was statistically significant in EDITION 1 and EDITION 2 but not in EDITION 3. At 6 months, the mean basal insulin dose was approximately 12% higher with insulin glargine 300 units/ml than with insulin glargine 100 units/ml. The mean basal insulin dose at month 6 was reported as 0.85 units/kg/day with insulin glargine 300 units/ml and 0.76 units/kg/day with insulin glargine 100 units/ml. The dose of insulin glargine 300 units/ml was 10% higher in EDITION 1 and EDITION 2, and 17% higher in EDITION 3. The authors concluded that a similar reduction in HbA1c was seen from baseline to month 6 and that non-inferiority was demonstrated between the two products.

Data from the head to head trials, CONCLUDE and BRIGHT and retrospective analyses from the DELIVER programme, 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 glycaemic control with both treatments. Further data is required, particularly in relation to the comparative differences if any, of insulin degludec 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 these trials and analyses are inconsistent and conflicting.

Cost effectiveness

There appears to be no cost effectiveness data based on the United Kingdom National Health Service perspective for insulin glargine 300 units/ml.

A cost effectiveness study has been published utilising data comparing insulin degludec with insulin glargine 100 units/ml from the perspective of the NHS in England. Treatment with insulin degludec was associated with a mean 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. The higher acquisition costs with insulin degludec were 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 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.

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 glargine 300 units/ml and insulin degludec, 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 glargine 300 units/ml 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 formulations 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.