Insulin glargine 300 units/ml (Toujeo®)

Recommendations for use in adults

1. Insulin glargine 300units/ml (Toujeo®) is NOT RECOMMENDED for routine use in either type 1 or type 2 diabetes in primary and secondary care due to current patient safety concerns with the use of high strength insulins.
2. CCGs and Area Prescribing Committees are advised to the consider the place in therapy, 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 hyperosmolar non–ketotic diabetic state or hyper HONK) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.
   - Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA or HHS if daily basal insulin is missed.
   - Patients with a diagnosed allergy to either insulin detemir or insulin degludec.
4. Insulin glargine 300units/ml (Toujeo®) could be considered for patient with mild to moderate insulin resistance (≥1-2units/kg/day) when treatment is initiated by a consultant Diabetologist.

   Patients with severe insulin resistance requiring very large daily doses of insulin (≥3units/kg/day) could be considered for Insulin glargine 300units/ml (Toujeo®) when 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.
6. Insulin glargine 300 units/ml (Toujeo®) 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. Any further adjustments in dose should be under the supervision of the specialist team.
8. 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.
9. These recommendations will be reviewed in the light of new evidence on clinical, cost effectiveness and safety.

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 but with a pharmacokinetic profile broadly similar to insulin degludec. Unlike insulin degludec, insulin glargine 300 units/ml is only licensed for use in adult patients over the age of 18 years at present; whereas insulin degludec is licensed in adults and children over one year of age.
- 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 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, of 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 nine and month six was lower with glargine 300 units/ml compared with glargine 100 units/ml; 36% with glargine 300 units/ml and 46% with glargine 100 units/ml (relative risk [RR] 0.79; 95% CI 0.67 to 0.93, p=0.0045) in EDITION 1; 22% with glargine 300 units/ml and 28% with glargine 100 units/ml (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) and 16% with glargine 300 units/ml and 17% with glargine 100 units/ml; (RR 0.89; 95% CI 0.66 to 1.20), in EDITION 2 and EDITION 3 respectively. This was statistically significant in EDITION 1 and EDITION 2 but not in EDITION 3.
- 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 what its effect is on macrovascular or microvascular outcomes.
- There is limited comparative evidence with other insulins or with continuous subcutaneous insulin pumps.
- There is limited long term safety data beyond 12 months.
- 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.
- NICE have produced two evidence summaries in relation to insulin glargine 300units/ml (Toujeo®), however there are no specific NICE technology appraisals or guidelines regarding insulin glargine 300 units/ml at present.
- The Scottish Medicines Consortium has accepted the use of insulin glargine 300 units/ml in restricted categories of patients only.
- Insulin glargine 300 units/ml currently has a higher cost than biphasic insulin and other analogue insulins.
- Insulin glargine 300 units/ml is equivalent in cost to glargine 100 units/ml (Lantus®) preparations.
- Insulin glargine 300 units/ml may offer few or no meaningful advantages for the majority of potential users but may be suitable for a small subgroup of patients, similar to the PAC recommendations for the use of insulin degludec. Feedback from East of England clinicians indicates that they have found insulin glargine 300 units/ml (Toujeo®) of benefit for some patients in these clinical groups who have not responded to insulin degludec.
- The higher-strength insulins may also be useful in patients who would otherwise require a large dose volume or multiple injections to obtain their required dose (i.e. patients requiring more than three 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 and Area Prescribing Committees consider the place in therapy, safety and implementation issues locally, with respect to formulary positioning and suitability for prescribing in primary care.

Proposed sector of prescribing: Primary and secondary care

Introduction

Diabetes mellitus is a group of metabolic disorders, in which persistent hyperglycaemia is caused by deficient insulin secretion, or by resistance to the actions of insulin, often combined with relative insulin deficiency. Insulin deficiency and insulin resistance leads to the abnormalities of carbohydrate, fat, and protein metabolism that are characteristic of diabetes mellitus.[1-3] Subcutaneous insulin is used in type 1 and type 2 diabetes mellitus to control blood sugar and symptoms.

The National Institute for Health and Care Excellence (NICE) currently recommends a basal-bolus insulin regimen.[4] This involves using longer acting insulin (basal or background insulin) to keep blood glucose levels stable through periods of fasting and separate injections of shorter acting insulin to prevent rises in blood glucose levels resulting from meals. Intermediate insulins such as NPH or isophane, or the newer long acting insulin analogues such as insulin detemir, insulin glargine 100 units/ml or insulin degludec are commonly used as the basal component.

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It 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 smooth, peak less, predictable concentration/time profile with a prolonged duration of action.[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®),[6] 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), as demonstrated by several small euglycaemic clamp studies.[7-14] The more sustained release of insulin glargine 300 units/ml from the Toujeo® precipitate compared to insulin glargine 100 units/ml is attributable to the reduction of the injection volume by two thirds which results in a smaller precipitate surface area.[7] Insulin glargine 300 units/ml has a much slower onset of action compared to both insulin glargine 100 units/ml and insulin degludec, and once at steady state, insulin glargine 300 units/ml has a 27% lower ability compared with insulin glargine 100 units/ml to reduce blood glucose at equivalent weight based dosing.[7-14] The clinical significance of this is unclear.

See table 1 in appendix 1, for comparative information in relation to pharmacokinetic parameters of insulin glargine 300 units/ml and other insulins.

Evidence: Insulin glargine 300 units/ml (Toujeo®)

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.[7,15-21]

Type 1 diabetes

In EDITION-4, a phase-3, randomised, 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.[15] The primary end-point was HbA1c at six months.

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 six 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 six; 16.8% with glargine 300 units/ ml and 15.0% with glargine 100 units/ml respectively.[15]

Rates of hypoglycaemia did not differ between treatment groups at six months. In the glargine 300

units/ ml group, 93.1% of participants had one or more confirmed or severe hypoglycaemic events over six months compared with 93.5% in the glargine 100 units/ml group; (relative risk [RR] 1.00; 95% CI 0.95 to 1.04).[15] Nocturnal hypoglycaemic events occurred in 68.6% of the glargine 300 units/ml group and 70.2% of the 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 glargine 300 units/ml group and 9.5% of the glargine 100 units/ml group; (RR 0.71; 95% CI 0.41 to 1.24). At six months, the basal insulin dose was approximately 18% higher with glargine 300 units/ml (0.47 units/kg/day) than with glargine 100 units/ml (0.40 units/kg/day).[15]

A case report published in 2016, highlights the experience of a 28-year patient with type 1 diabetes, prescribed insulin glargine 100 units/ml from July 2015 to November 2015. During this period, he experienced on average 4.8 hypoglycaemic (<3.9mmol/l events per week, with 1.5 per week being classified as severe; 89% occurred at night (between 21.00hrs and 09.00hrs). No very severe episodes were recorded. In November 2015, he was switched to insulin glargine 300 units/ml. By the end of February 2016, the number of hypoglycaemic events had dropped to 2.3 per week, with 0.4 per week being classed as severe; 70% occurred at night. Daily blood glucose was 6.8 mmol vs. 6.9 mmol with 100 units/ml and U 300 respectively and HbA1Ac was 41mmol/mol versus 42 mmol/mol.[22]

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;[16-21]

- EDITION 1: involved 807 adults using basal and mealtime insulin[16-17]
- EDITION 2: involved 811 adults who were also using oral blood glucose lowering drugs and basal insulin[18-19]
- EDITION 3: involved 878 insulin naïve adults.[20]

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.

No difference was reported between groups in EDITION 1; [95% CI −0.11 to 0.11%, −1.2 to 1.2mmol/mol]. 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.[16-20] 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 six.

The percentage of participants experiencing, at least one confirmed or severe nocturnal hypoglycaemic event between week nine and month six was lower with glargine 300 units/ml compared with glargine 100 units/ml in the three trials: 36% with glargine 300 units/ml and 46% with glargine 100 units/ml (RR 0.79; 95% CI 0.67 to 0.93, p=0.0045) in EDITION 1; 22% with glargine 300 units/ml and 28% with insulin glargine 100 units/ml (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) in EDITION 2 and 16% with glargine 300 units/ml and 17% with glargine 100 units/ml; (RR 0.89; 95% CI 0.66 to 1.20) in EDITION 3. The study authors cited that the results were statistically significant in EDITION 1 and but not in EDITION 3, however it is not clear from the study description if possible lack of patient numbers in this group has reduced the reliability of assessment of the secondary endpoint at six months. The mean basal insulin dose was approximately 12% higher with glargine 300 units/ml than with glargine 100 units/ml. The mean basal insulin dose at month six was reported as 0.85 units/kg/day with glargine 300 units/ml and 0.76 units/kg/day with glargine 100 units/ml. The dose of glargine 300 units/ml was 10% higher in EDITION 1 and EDITION 2, and 17% higher in EDITION 3.[16-20] The authors concluded that a similar reduction in HbA1c, was seen from baseline to month six and that non-inferiority was demonstrated between the two products.

Severe nocturnal hypoglycaemic events were reported as rare in all three RCTs but too few for a meaningful analysis to be completed in each trial.[16-20]

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 glargine 300 units/ml group and 2.6% in the glargine 100 units/ml group (RR 0.85, 95% CI 0.52 to 1.39).

In a post-hoc meta-analysis of the three RCTs,[21] the annualised rate of confirmed or severe nocturnal

events over the six month study period was 31% lower with glargine 300 units/ml compared with glargine 100 units/ml (2.10 events per participant-year with glargine 300 units/ml versus 3.06 events per participant-year with glargine 100 units/ml; RR 0.69, 95% CI 0.57 to 0.84, p=0.0002).[21] 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 limited direct comparative evidence with insulin degludec or other basal insulins. In a small double-blind cross over study, 57 patients randomly received either insulin degludec or insulin glargine 300 units/ml over two treatment periods, lasting 12 days each. Pharmacodynamic variables were assessed at steady state from glucose infusion rate profiles of three 24-hour euglycaemic glucose clamps at days six, nine and 12 during each treatment period. The potency of glargine 300 units/ml was 30% lower than degludec (estimated ratio 0.70, 95% CI 0.61; 0.80; p<0.0001). The distribution of glucose-lowering effect was stable across six-hour intervals (24%-26%) for degludec, while glargine 300 units/ ml had greater effects in the first (35%) and last (28%) intervals compared with six to 12 hours (20%) and 12 to 18 hours (17%). Within-day variability (relative fluctuation) was 37% lower with degludec than with glargine 300 units/ml (estimated ratio degludec/ glargine 300 units/ml: 0.63, 95% CI 0.54; 0.73; p<0.0001). The day-to-day variability in glucose-lowering effect with degludec was approximately 4 times lower than glargine 300 units/ml (variance ratio glargine 300 units/ml/ degludec: 3.70, 95% CI 2.42; 5.67; p<0.0001). The day-to-day variability in glucose-lowering effect assessed in two-hour intervals was consistently low with degludec over 24 hours, but steadily increased with glargine 300 units/ml to a maximum at 10 to 12 hours and 12 to 14 hours after dosing (variance ratios 12.4 and 11.4, respectively). The study authors concluded that insulin degludec had lower day to day and within day variability than glargine 300 units/ml and a more stable glucose lowering effect.[22]

A network meta-analysis was published in 2016, which 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 studies comprising the main analysis population of patients on basal insulin-supported oral therapy (BOT). The analysis reported that the change in glycated haemoglobin (HbA1c) was comparable between glargine 300 units/ml and detemir (difference −0.08; −0.40 to 0.24), neutral protamine Hagedorn (NPH 0.01; −0.28 to 0.32), 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 detemir (0.69; −0.31 to 1.71), NPH (−0.76; −1.75 to 0.21) and 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 (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 detemir (0.52; 0.19 to 1.36) and degludec (0.66; 0.28 to 1.50). Differences in documented symptomatic hypoglycaemia rates of insulin glargine 300 units/ml versus detemir (0.63; 0.19 to 2.00), NPH (0.66; 0.27 to 1.49) and degludec (0.55; 0.23 to 1.34) were not statistically significant. The analysis authors concluded that glargine 300 units/ml is also associated with a significantly lower risk of nocturnal hypoglycaemia compared with NPH and premixed insulin, with glycaemic control comparable to available basal insulin comparators.[23]

A trial comparing efficacy and health outcomes of insulin glargine 300 units/ml with other long acting basal insulins (insulin glargine 100 units/ml and insulin determir) is currently underway in insulin naïve patients with type 2 diabetes; n=3270).[24]

Long term data

There is limited data beyond 12 months for insulin glargine 300 units/ml.[25-27]

Data from six month extension studies, in which patients continued to receive their originally assigned treatment, and a pooled analysis, suggest that efficacy of glargine 300 units/ml is maintained in the longer term, with reductions in HbA1c and fasting blood glucose levels being sustained over 12 months.
In EDITION 1, the mean change from baseline in HbA1c was greater with glargine 300 units/ml than with glargine 100 units/ml (-0.86 vs. -0.69; p=0.007) and in the pooled analysis of EDITION 1, 2 and 3 (-0.91% vs. -0.80%; p=0.0174).[25] Corresponding changes in HbA1c in EDITION 2 were -

0.55% and -0.50% respectively.[26] Mean weight gain was lower in glargine 300 units/ml recipients than in glargine 100 units/ ml recipients (+0.4 kg vs. +1.2 kg; p=0.009) in EDITION 2[26] and in the pooled analysis of EDITION 1, 2 and 3 (+1.2 vs. +1.5 kg; p=0.0117).[27] In EDITION 1, the mean change in bodyweight from baseline was + 1.2 and +1.4 kg in the respective treatment groups.[27]

At the time of writing, similar long term data in type 1 patients from EDITION 4 had not been published.

Adverse events

The European Product Assessment Report (EPAR)[8] produced for the licensing process, states that the safety profile of insulin glargine 300 units/ml (insulin glargine 300 units/ml) is similar to that of insulin glargine 100 units/ml (Lantus®) and no additional safety signals were detected. The most frequent adverse events were nasopharyngitis (8.2% with insulin glargine 300 units/ml; 6.8% with insulin glargine 100 units/ml (Lantus®)) and upper respiratory tract infection (6.5% with insulin glargine 300 units/ml, 5.8% with insulin glargine 100 units/ml (Lantus®)). Most of the adverse events were mild to moderate in intensity. Overall, serious adverse events were reported by 5.4% of people in both insulin glargine 300 units/ml and insulin glargine 100 units/ml groups; most commonly hypoglycaemia in people with type-1 diabetes.[8]

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.[13,28]

Evidence strengths and limitations

- Insulin glargine 300 units/ml has been shown to be non-inferior to insulin glargine 100 units/ml. There are no superiority trials.
- There is limited comparative evidence with other insulins including insulin degludec. There are no trials comparing it to Neutral Protamine Hagedorn (NPH) insulin or other insulins
- There is no evidence to confirm that insulin glargine 300 units/ml use is associated with a reduction in hospital admissions for diabetes related complications or mortality.
- There are no patient-oriented outcome data for the effects of insulin glargine 300 units/ml on macrovascular or microvascular outcomes.
- There is limited long term safety data beyond 12 months.
- There is no evidence which directly compares insulin glargine 300 units/ml with subcutaneous insulin pumps.
- There is a lack of data in patients with renal or hepatic impairment; frequent monitoring and dose adjustment may be required. Due to progressive deterioration in of renal function, insulin requirements may be reduced in patients over the age of 65 years. Caution is recommended in elderly patients.

Implementation considerations

Insulin glargine 300 units/ml (Toujeo®) is licensed for the treatment of type 1 and type 2 diabetes mellitus in adults only.[7] It is not currently licensed for use in children and adolescents. This is different to both insulin glargine 100 units/ml (Lantus®) which is licensed for the treatment of diabetes mellitus in adults, adolescents and children aged two years and above[5] and insulin degludec (Tresiba®) which is licensed for the treatment of diabetes mellitus in adults, adolescents and children from the age of one year.[29]

Insulin glargine 300 units/ml is indicated for once-daily subcutaneous administration at the same time each day.[7,14] When necessary, insulin glargine 300 units/ml may be administered up to three hours before or after the usual time of administration.[7,14] Injection-site rotation within the same region (deltoid, abdominal wall or thigh) is recommended to reduce the risk of lipodystrophy.[7,14] 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.[7] Insulin glargine 300 units/ml can be administered in combination with other glucose-lowering medications in patients with type 2 diabetes.[7]

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.[7,14,30,31]

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 that the dose may need to be adjusted to achieve target plasma glucose level ranges.[32] Data from the EDITION trials suggest that patients switching from insulin glargine 100 units/ml may require a higher daily dose of insulin glargine 300 units/ml to achieve the same glycaemic control. The recommended starting dose of insulin glargine 300 units/ml in insulin-naïve patients with type 1 diabetes is approximately 33–50% of the total daily insulin requirements or a starting dose of 0.2–0.4 unit/kg/day is recommended with the continuation of mealtime insulin. A starting dose of 0.2 unit/kg/day is recommended for insulin-naive patients with type 2 diabetes.[7,14]

In insulin-experienced patients, switching to insulin glargine 300 units/mL from a once-daily intermediate or long acting insulin can be done on a unit-to-unit basis.[11,32]

However, the following additional advice is provided by the manufacturer. When switching from twice-daily NPH insulin, the recommended starting dose of glargine 300 units/ml is 80% of the total daily insulin dose.[7,14] The dose of glargine 300 units/ml should be adjusted according to individual patient needs. After initiation of glargine 300 units/ml, the dose should not be adjusted for one week, as steady state is achieved in an average of 6.6 days.[7,14] Once steady state is achieved, adjustment of the glargine 300 units/ml dose can occur every three to four days. The manufacturer does not provide a conversion from premixed insulin or insulin degludec, insulin determir, and there were no participants converting from premixed insulin or longer acting insulins to insulin glargine 300 units/ml in the EDITION trials.[7,14-20]

High strength insulin products have been associated with a possible increase risk of medication errors.[32] A Medicines and Healthcare Regulatory Agency (MHRA) Drug Safety Update has been issued with advice for healthcare professionals to minimise risk of errors with the two strengths, including risk assessment of clinical storage areas.[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. All patients should be closely monitored, particularly at the start of treatment and when the dose or type of insulin changes as absorption and response can vary greatly between patients. Initial dose titration and monitoring should take place under the close supervision of a specialist team.[31] The strength of the insulin formulation should always be included on the prescription. 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.[31-33]

All insulins, including insulin glargine formulations, should be prescribed by brand name.[31-33]

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.

Insulin glargine 300 units/ml is supplied in a prefilled pen device (for safety purposes). Each pen contains 450 units of insulin glargine. The insulin glargine 300 pre-filled pen can deliver a dose of 1 to 80 units in one injection, in increments of 1 unit. It has the same administration, storage, and expiration instructions as insulin glargine 100 units/ml.

A NHS Improvement patient safety alert, published in November 2016,[34] 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.

Insulin should never be extracted from insulin pen devices.[34]

Comparative costs (eMIMs and eBNF)

Comparative costs are shown in table 2, in appendix 1.[6,35]

Insulin glargine 300 units/ml is currently higher cost than biphasic insulin and some analogue basal insulins. Insulin glargine 100 units/ml is included in the PbR tariff.[36] Table 2 shows cost per year based on 30 units per day.

Whilst insulin glargine 300 units/ml appears to be cheaper than glargine 100 units/ml (Lantus®), in the clinical trials a 10-18% increase in dose was required compared to glargine 100 units/ml, with the overall cost being similar.

The estimated activity costs for an uncontrolled diabetic, experiencing severe hypoglycaemic episodes which result in at least one hospital admissions per month, is approximately £18,000 per year.[36]

There appears to be no cost effectiveness data based on the United Kingdom National Health Service perspective. A cost utility evaluation based on Spanish data suggests that insulin glargine 300 units/ml may be associated with an incremental QALY gain compared to insulin glargine 100 units/ml based on the reduction in nocturnal hypoglycaemic events and dosing flexibility.[37]

In a Canadian study involving 231 type 1 and 1028 type 2 diabetes patients, who were switched from standard basal insulin to insulin glargine 300 units/ml and followed for 12 months, the average daily dose of insulin reduced from 88 units to 73 units insulin glargine 300 units/ml in type 1 patients and from 111 units to 98 units in type 2 patients.[38]

Place in therapy

Insulin glargine 300 units/ml (Toujeo®) is only currently licensed in adults over the age of 18 years. It is not licensed in children in adolescents.

NICE evidence summaries are available for insulin glargine 300 units/ml.[38,40] There are no technology appraisals available and insulin glargine 300 units/ml is not in the NICE technology appraisal work programme. No specific recommendation in relation to insulin glargine 300 units/ml is included in any of the current NICE clinical guidance.[4,41-42]

NICE clinical guidance (NG28) for type 2 diabetes recommends isophane (NPH) insulin including biphasics, first line for patients who remain uncontrolled despite optimised treatment with oral hypoglycaemics.[41]

NICE clinical guideline (NG17) for type 1 diabetes in adults suggests that basal insulin other than (insulin glargine or insulin determir), can be considered in patients where agreed targets are not being met.[4]

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.[43]

There is no information regarding insulin glargine 300 units/ml on the All Wales Medicines Strategy Group (AWMSG) website.

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.[44]

The use of the higher strength insulins, such as insulin glargine 300 units/ml are not routinely recommended, but could be considered in patients receiving large daily doses of standard insulins (≥3

units/kg/day),[45] following referral to tertiary centre for severe insulin resistance, where treatment is initiated by a Consultant Diabetologist.

Insulin resistance services are NHSE commissioned, however prescribing for medicines initiated under the service is transferred to CCGs after three months.[46]

CCGs 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.

This document has been adapted from the East of England Priorities Advisory Committee, with thanks and acknowledgement to the author Vicky Gibson on behalf of East of England Priorities Advisory Committee. Approved MOPB June 2018 Review 2020

Document history

PAC approval date	8 January 2018	**Version**	1.1
Document history	v1.1 - May 2018 Updated information on pen device and dose delivery		
Consultation process	PAC members East of England clinicians		
QA process	Katie Smith, Senior Clinical Pharmacist, PrescQIPP - 26th February 2018		
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 data

Table 1: Comparative information in relation to pharmacokinetic parameters of insulin glargine 300 units/ml and other insulins

Brand name	Brand name	Generic name	Onset	Peak	Duration
Bolus insulin	Actrapid	Soluble or neutral insulin	<30min	1.5-3.5	7-8hr
	Humulin S	Soluble or neutral insulin	30min-1hr	1-6hr	6-12hr
	Insuman Rapid	Soluble or neutral insulin	<30min	1-4hr	7-9h
Rapid acting - bolus insulin	Novorapid	Insulin aspart	10-20min	1-3hr	3-5hr
	Humalog	Insulin lispro	15min	1.5hr	2-5hr
	Fiasp	Insulin aspart	4min	1-3hr	3-5hr
	Apidra	Insulin glulisine	10-20 min	55 min	1.5-4hr
Basal insulin	Humulin I	Isophane insulin (NPH insulin)	30min-1hr	1-8hr	22hr
	Insulatard	Isophane insulin (NPH insulin)	<1.5hr	4-12hr	24hr
	Insuman Basal	Isophane insulin (NPH insulin)	<1hr	3-4hr	11-20hr
Basal - insulin analogues	Lantus	insulin glargine 100 units/ml	1-4hr	-	24hr
	Abasaglar	Insulin glargine - biosimilar 100 units/ml	1-4hr	-	24hr
	Levemir	Insulin determir	30min-1hr	-	24hr
Basal - ultra long acting insulin	Tresiba	Insulin degludec 100 units/ml	1-2hr	-	>42hr
High strength basal insulin (concentrated)	Toujeo	Insulin glargine 300 units/ml	1-6hr	-	24-36hr
	Tresiba	Insulin degludec U200	1-2hr	-	>42hr
	Humulin R (Imported from US- unlicensed in	Insulin human injection, USP	30-45min	4-8hr	12-24hr
Biphasic or premixed insulins	Humulin M3 70/30	Insulin NPH + neutral insulin	30min-1hr	1-12hr	22hr
	Humalog Mix	Insulin lispro + insulin lispro protamine	15min	2hr	22hr
	Novomix	Insulin aspart + insulin aspart protamine	10-20 min	1-4hr	24hr
	Insuman Comb	Neutral insulin + isophane insulin	30min-1hr	2-4hr	11-20hr

Table 2: Comparative costs for long acting basal analogue insulins

Brand name		Generic name	Cost per pack	Cost per	Cost for 30 units	Cost per 28	Cost per year
Basal insulin	Humulin I	Isophane Insulin (NPH	£21.70	£0.014	£0.43	£12.18	£158.00
	Insulatard	Isophane Insulin (NPH	£20.40	£0.014	£0.41	£11.42	£148.51
	Insuman Basal	Isophane Insulin (NPH	£19.80	£0.013	£0.40	£11.09	£144.14
Basal - insulin analogues	Lantus	Insulin glargine 100	£41.50	£0.03	£0.83	£23.24	£302.12
	Abasaglar	Insulin glargine - biosimilar 100 units/ml	£35.28	£0.02	£0.71	£19.76	£256.84
	Levemir	Insulin determir	£42.00	£0.03	£0.84	£23.52	£305.76
Basal - ultra long acting insulin	Tresiba	Insulin degludec 100 units/ml	£46.60	£0.03	£0.93	£26.10	£339.25
High strength basal insulin (concentrated)	Toujeo	Insulin glargine 300	£33.13	£0.02	£0.80	£22.40	£291.20
	Tresiba	Insulin degludec 200	£55.92	£0.03	£0.93	£26.10	£339.25
	Humulin R (Imported from US - unlicensed in	Insulin human injection,				£211*	£274
Biphasic or premixed insulins	Humulin M3 70/30	Insulin NPH + neutral insulin	£21.70	£0.014	£0.43	£12.18	£158.00
	Humalog Mix	Insulin lispro + insulin lispro	£29.46	£0.02	£0.59	£16.50	£214.47
	Novomix 30	Insulin aspart insulin aspart + protamine	£28.79	£0.02	£0.58	£16.12	£209.59
	Insuman Comb	Neutral insulin + isophane insulin	£19.80	£0.013	£0.40	£11.09	£144.14

Appendix 2: Assessment against ethical and commissioning principles

1. Treatment assessed

Insulin glargine 300 units/ml (Toujeo®)

2. 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 in primary and secondary care due to current patient safety concerns with the use of high strength insulins.

CCGs 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.

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 patients with type 1 or type 2 diabetes who fulfil the following criteria:

Patient with significant hypoglycaemia, despite optimal adjustments of lifestyle (eliminating any contributory factors), diet (undertaken structured education e.g. DAFNE), and basal insulin/multiple daily injections and who fulfil the criteria for insulin pump therapy.

“Chaotic patient” who may be at significant risk of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) (previously known as hyperosmolar non – ketotic diabetic state or hyper HONK) if daily basal insulin is missed, despite optimal adjustments of lifestyle, and diet and optimising basal insulin/multiple daily injections.

Patients with psychological problems (e.g. eating disorders or patients with intermittent compliance issues with insulin injections), who are not supervised by a daily carer and do not qualify to receive district nurse injections of daily insulin glargine, and who may be at significant risk of DKA or HHS if daily basal insulin is missed.

Patients with a diagnosed allergy to either insulin detemir or insulin degludec.

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

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.

3. 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-3, randomised, 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 HbA1c at six months. 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 six 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 six; 16.8% with glargine 300 units/ml and 15.0% with glargine 100 units/ml respectively.[15] Rates of hypoglycaemia did not differ between treatment groups at six 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 EDITION1; [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 [16-20]. These differences were all below the pre-specified non- inferiority margin of 0.4%. At month six, 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 nine and month six was lower with glargine 300 units/ml compared with glargine 100 units/ml. 36% with glargine 300 units/ml and 46% with glargine 100 units/ml (relative risk [RR] 0.79; 95% CI 0.67 to 0.93, p=0.0045) in EDITION 1; 22% with glargine 300 units/ml and 28% with insulin glargine 100 units/ml (RR 0.77; 95% CI 0.61 to 0.99, p=0.038) in EDITION 2 and 16% with glargine 300 units/ml and 17% with glargine 100 units/ml (RR 0.89; 95% CI 0.66 to 1.20) in EDITION 3 respectively. This was statistically significant in EDITION 1 but not in EDITION 3. At six months, the mean basal insulin dose was approximately 12% higher with glargine 300 units/ml than with glargine 100 units/ml. The mean basal insulin dose at month six was reported as 0.85 units/kg/day with glargine 300 units/ml and 0.76 units/kg/day with glargine 100 units/ml. The dose of glargine 300 units/ml was 10% higher in EDITION 1 and EDITION 2, and 17% higher in EDITION 3.[16-20] The authors concluded that a similar reduction in HbA1c was seen from baseline to month six and that non-inferiority was demonstrated between the two products.

4. Cost effectiveness

No UK health economy studies identified. 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 degludec would be reduced as this has not been studied.

5. Equity

No issues identified.

6. 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.

7. Need for healthcare

The needs of the population appear to be low as there are available alternative treatment options recommended within local guidelines and by NICE. However, specialists have highlighted a cohort of patients with sub-optimal control who may benefit from treatment with insulin degludec or insulin glargine 300 units/ml®.

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

8. Policy drivers

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

9. Disinvestment

Possible alternative to insulin degludec and the imported high strength Humulin R, in adults only.