NICE National Institute for Health and Care Excellence

NICE advice

Type 2 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo)

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in December 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

High-strength insulin products such as insulin glargine 300 units/ml (Toujeo) have been developed for people with type 1 or type 2 diabetes who have large daily insulin requirements to reduce the number and volume of injections. In 3 randomised controlled trials (RCTs) in 2496 adults with type 2 diabetes, Toujeo had similar efficacy to insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction. There was a statistically significant reduction in confirmed or severe nocturnal hypoglycaemia with Toujeo in 2 of the RCTs, but not in the third trial. Severe hypoglycaemic events were rare and not

statistically significantly different between Toujeo and Lantus. The safety profile of Toujeo is largely similar to that of Lantus. Toujeo is not bioequivalent to Lantus and they are not interchangeable without dose adjustment. An evidence summary on Toujeo in type 1 diabetes has also been published.

Regulatory status: insulin glargine 300 units/ml (Toujeo) received a European marketing authorisation in April 2015. It was launched in the UK in August 2015.

Effectiveness	**Safety**
• Once-daily Toujeo was non-inferior to once-daily Lantus in HbA1c reduction from baseline to month 6 (difference between groups 0.00% [0.00 mmol/mol], 95% confidence interval [CI] –0.08 to 0.07% [–0.9 to 0.8 mmol/mol]) in adults with type 2 diabetes (meta-analysis of 3 RCTs, n=2496). • The percentage of adults with confirmed or severe nocturnal hypoglycaemia was lower with Toujeo than with Lantus in 2 of the 3 RCTs (36% versus 46%, p=0.0045 and 22% versus 28%, p=0.038) but not in the third trial (16% versus 17%, not statistically significant). • At 6 months the basal insulin dose was approximately 12% higher with Toujeo than with Lantus (meta-analysis of 3 RCTs, n=2496).	• The safety profile of Toujeo is largely similar to that of Lantus. The most frequent adverse events are nasopharyngitis and upper respiratory tract infection; the most frequent severe adverse event is hypoglycaemia (European public assessment report [EPAR] for Toujeo). • In 3 RCTs (n=2496), similar numbers of participants reported injection site reactions with Toujeo (2.4%) and Lantus (3.1%), and similar numbers withdrew because of adverse events (1.4% with Toujeo and 1.3% with Lantus).

Patient factors	Resource implications
• Toujeo is a high-strength insulin. It is not simply interchangeable with other long-acting insulins and there is a potential risk of medication error. However, the dose window of the Toujeo pen shows the number of Toujeo units to be injected. Patients should read and understand the patient leaflet and education material and should have training on the correct use of Toujeo. • Toujeo is given once daily, preferably at the same time each day but can be up to 3 hours before or after usual time. • There was a reduction of approximately 1 confirmed or severe nocturnal event per person per year with Toujeo compared with Lantus. Severe hypoglycaemic events were rare and not statistically significantly different between Toujeo and Lantus (meta-analysis of 3 RCTs, n=2496) • Body weight increased less with Toujeo than with Lantus (mean increase at 6 months 0.51 kg compared with 0.79 kg; p=0.039; meta-analysis of 3 RCTs, n=2496). • The higher concentration of insulin in Toujeo means the volume to be injected is smaller, which may be less painful for people injecting large volumes.	• The cost of Toujeo and other basal insulins will depend on the preparation chosen and the insulin dosage used. • The manufacturer has stated that Toujeo has been priced at a level to match the daily cost of Lantus on the basis of average insulin glargine usage in the EDITION trials. The cost of Toujeo is £33.13 for 3×1.5 ml pre-filled pens (excluding VAT; MIMS, November 2015).

Introduction and current guidance

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2

diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. The updated NICE guideline on type 2 diabetes in adults: management recommends adopting an individualised approach to diabetes care.

Full text of introduction and current guidance.

Product overview

Toujeo is a high-strength insulin glargine product containing 300 units/ml solution for injection in a pre-filled pen (Toujeo Summary of Product Characteristics). It is a basal insulin for once-daily use for the treatment of diabetes mellitus (type 1 and type 2) in adults. In people with type 2 diabetes, it can be given together with other anti-hyperglycaemic medicinal products.

Toujeo is not bioequivalent to insulin glargine 100 units/ml (Lantus) and dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa (MHRA Drug Safety Update April 2015). Toujeo has a flatter and more prolonged (up to 36 hours) profile of insulin concentration and glucose lowering activity compared with Lantus at the same doses (European public assessment report [EPAR] for Toujeo).

Toujeo is available in a pack containing 3 pens. Each pen contains 1.5 ml of insulin glargine 300 units/ml solution for injection, equivalent to 450 units. The cost of a pack of 3 pens is £33.13 (excluding VAT; MIMS, November 2015).

Full text of product overview.

Evidence review

This evidence summary is based on the 3 main phase 3 studies of Toujeo in adults with type 2 diabetes (EDITION 1, EDITION 2 and EDITION 3). EDITION 1 was in adults with type 2 diabetes who were using basal and mealtime insulin. In EDITION 2, adults with type 2 diabetes were using oral blood glucose lowering drugs and basal insulin; and in EDITION 3, adults with type 2 diabetes were insulin-naive. The objective of these RCTs was to demonstrate that insulin glargine 300 units/ml (Toujeo) is non-inferior to insulin

glargine 100 units/ml (Lantus) in terms of HbA1c reduction and, based on its pharmacodynamic and pharmacokinetic profiles, is associated with a lower risk of hypoglycaemia. The main phase 3 study of Toujeo in adults with type 1 diabetes (EDITION 4) is reviewed in the evidence summary on type 1 diabetes.

- In EDITION 1 (n=807), EDITION 2 (n=811) and EDITION 3 (n=878), once-daily insulin glargine 300 units/ml (Toujeo) was non-inferior to once-daily insulin glargine 100 units/ml (Lantus) in adults with type 2 diabetes. A similar reduction in HbA1c from baseline to month 6 was seen in both treatment groups in each study. In EDITION 1 the difference between groups was 0.00% [0.00 mmol/mol], 95% confidence interval [CI] −0.11 to 0.11% [−1.2 to 1.2 mmol/mol] in people who were already using basal and mealtime insulin at baseline. In EDITION 2 the difference was −0.01% [0.1 mmol/mol], 95% CI −0.14 to 0.12% [−1.5 to 1.3 mmol/mol] in people who were using oral blood glucose lowering drugs and basal insulin at baseline. In EDITION 3, in people who were insulin-naive at baseline, the difference was 0.04% [0.4 mmol/mol], 95% CI −0.09 to 0.17% [−1.0 to 1.9 mmol/mol]. 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.
- The percentage of participants experiencing at least 1 confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6 was statistically significantly lower with Toujeo compared with Lantus in EDITION 1 and EDITION 2, but not in EDITION 3:
  - 36% with Toujeo and 46% with Lantus in EDITION 1 (relative risk [RR] 0.79; 95% CI 0.67 to 0.93, p=0.0045)
  - 22% with Toujeo and 28% with Lantus in EDITION 2 (RR 0.77; 95% CI 0.61 to 0.99, p=0.038)
  - 16% with Toujeo and 17% with Lantus in EDITION 3 (RR 0.89; 95% CI 0.66 to 1.20)
  - severe nocturnal hypoglycaemic events were rare in all 3 RCTs and too few for meaningful analysis in each trial.

- In a post-hoc meta-analysis of the 3 RCTs (Ritzel et al 2015), the annualised rate of confirmed or severe nocturnal events over the 6-month study period was 31% lower with Toujeo compared with Lantus (2.10 events per participant-year with Toujeo and 3.06 events per participant-year with Lantus; RR 0.69, 95% CI 0.57 to 0.84, p=0.0002). This is a reduction of approximately 1 confirmed or severe nocturnal event per person per year, which is of debatable clinical significance. Severe hypoglycaemic events at any time of day were rare and not statistically significantly different between groups; the percentage of participants experiencing at least 1 severe event at any time of day was 2.3% in the Toujeo group and 2.6% in the Lantus group (RR 0.85, 95% CI 0.52 to 1.39).

- At 6 months the basal insulin dose was approximately 12% higher with Toujeo than with Lantus in a meta-analysis of the 3 RCTs in adults with type 2 diabetes (Ritzel et al 2015). The mean basal insulin dose at month 6 was 0.85 units/kg/day with Toujeo and 0.76 units/kg/day with Lantus. The dose of Toujeo was 10% higher in EDITION 1 and EDITION 2, and 17% higher in EDITION 3.

- In the 3 RCTs in adults with type 2 diabetes, the number of participants with any adverse event or any serious adverse event was similar in the Toujeo and Lantus groups. Body weight increased with both Toujeo and Lantus, but at month 6 the mean increase was smaller with Toujeo (0.51 kg) than with Lantus (0.79 kg; p=0.039).

- The EPAR states that the safety profile of Toujeo is largely similar to that of Lantus and no additional safety signals were detected. The most frequent adverse events were nasopharyngitis (8.2% with Toujeo, 6.8% with Lantus) and upper respiratory tract infection (6.5% with Toujeo, 5.8% with Lantus). Most of the adverse events were mild to moderate in intensity. Events of severe intensity were reported in 5.1% of the Toujeo group and 4.1% of the Lantus group, with the most frequent in both groups being hypoglycaemia (0.5% with Toujeo and 0.8% with Lantus).

- An important risk with high-strength insulin glargine 300 units/ml (Toujeo) is possible medication errors with other insulins of lower strengths. Toujeo is not bioequivalent to insulin glargine 100 units/ml (Lantus) and dose adjustment is needed. However, the dose window of the Toujeo pen shows the number of Toujeo units to be injected.

- The primary end point of the EDITION 1, 2 and 3 (total n=2496) was an HbA1c end point at 6 months. Extension studies to 12 months have been completed, and published for 2 of the RCTs. There are very limited patient-oriented outcome data for the effects of Toujeo on macrovascular or microvascular outcomes, and very limited long-term safety data for the 300 units/ml insulin glargine strength specifically.

Full text of evidence review.

Context

Basal insulin supply for adults with type 2 diabetes can be provided by:

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

Toujeo (insulin glargine 300 units/ml) is the third insulin to be approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. Insulin degludec (Tresiba) and insulin lispro (Humalog) are already available at a 200 units/ml strength.

The cost of Toujeo and other basal insulins will depend on the preparation chosen and the insulin dosage used. The manufacturer has stated that Toujeo has been priced at a level to match the daily cost of Lantus on the basis of average insulin glargine usage in the EDITION trials.

Full text of context.

Estimated impact for the NHS

High strength insulin products have been developed for people with large daily insulin requirements to reduce the number and volume of injections (MHRA Drug Safety Update April 2015). Specialists involved in the production of this publication have suggested that certain people with type 2 diabetes who are insulin resistant use very high basal insulin doses. In the phase 3 studies of Toujeo in adults with type 2 diabetes, the mean injection volume at 6 months was calculated to be 0.3 ml (77 units) with Toujeo and 0.8 ml (68 units) with Lantus for a 90 kg adult.

In the phase 3 studies of Toujeo in adults with type 2 diabetes (EDITION 1, EDITION 2 and EDITION 3), Toujeo had similar efficacy to Lantus in terms of HbA1c reduction. In 2 of the 3 studies, Toujeo statistically significantly reduced the risk of confirmed or severe nocturnal hypoglycaemia compared with Lantus (by about 1 event per person per year), but severe hypoglycaemic events were rare and not statistically significantly different between groups. The EPAR states that the more gradual glucose lowering effect of Toujeo

compared with Lantus did not translate into important advantages, and the higher use of basal insulin may be a disadvantage. In order to obtain a similar effect on HbA1c, on average 12% higher doses of Toujeo than Lantus were used in people with type 2 diabetes (Ritzel et al 2015).

The European Medicines Agency has recently consulted on guidance to minimise the potential risk of medication errors associated with the availability of high-strength insulins, such as Toujeo (MHRA Drug Safety Update April 2015).

Toujeo (insulin glargine 300 units/ml) is not simply interchangeable with other long-acting insulins, including insulin glargine 100 units/ml. When switching between Toujeo and other basal insulins, different doses may be needed to achieve target ranges for plasma glucose levels, giving rise to a potential risk of medication error. This risk is addressed in advice given in the summary of product characteristics, and educational material for healthcare professionals and patients has been produced as an additional risk minimisation measure.

The updated NICE guideline on type 2 diabetes in adults recommends that when insulin therapy is necessary, it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. Insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see the guideline for details). There are several insulin glargine products available including Lantus, the biosimilar Abasaglar or high-strength Toujeo).

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance and insufficient pancreatic insulin production, resulting in high blood glucose levels. Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure and disturbed blood lipid levels, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. Multiple vascular risk factors and wide-ranging complications make diabetes care complex and time-consuming, and many areas of healthcare services must be involved for optimal management. Necessary lifestyle changes, the complexities and possible side effects of therapy make patient education and self-management important aspects of diabetes care.

The updated NICE guideline on type 2 diabetes in adults: management recommends adopting an individualised approach to diabetes care that takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. The person's needs and circumstances should be reassessed at each review and consideration given to stopping any medicines that are not effective.

People with type 2 diabetes should be involved in decisions about their individual HbA1c target and be supported achieve and maintain this. For adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet in combination with a single drug not associated with hypoglycaemia, the guideline recommends supporting the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, the aim is an HbA1c level of 53 mmol/mol (7.0%). If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, advice about diet, lifestyle and adherence to drug treatment should be reinforced, the person supported to aim for an HbA1c level of 53 mmol/mol (7.0%) and drug treatment intensified. The target HbA1c level can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities.

The updated NICE guideline on type 2 diabetes recommends that when insulin therapy is necessary, it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. Insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see the guideline for details).

Product overview

Drug action

Insulin glargine is a human insulin analogue. Toujeo is a high-strength insulin glargine product containing 300 units/ml solution for injection in a pre-filled pen (Toujeo summary of product characteristics). It is a basal insulin for once-daily use.

Insulin glargine has the same metabolism after subcutaneous injection regardless of its source. The difference between insulin glargine 300 units/ml (Toujeo) and insulin glargine 100 units/ml comes only from the pharmacokinetic and pharmacodynamic profiles of the 2 formulations. Toujeo has a flatter and more prolonged (up to 36 hours) profile of insulin concentration and glucose lowering activity compared with Lantus at the same doses (European public assessment report [EPAR] for Toujeo).

Toujeo is not bioequivalent to Lantus and dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa (MHRA Drug Safety Update April 2015).

Licensed therapeutic indication

Insulin glargine 300 units/ml (Toujeo) is licensed for the treatment of diabetes mellitus in adults. In type 1 diabetes mellitus, it must be combined with short or rapid-acting insulin to cover mealtime insulin requirements. In people with type 2 diabetes mellitus, it can also be given together with other anti-hyperglycaemic medicinal products. This evidence summary covers the use of insulin glargine 300 units/ml in adults with type 2 diabetes. Another evidence summary covers its use in adults with type 1 diabetes.

Course and cost

Insulin glargine 300 units/ml (Toujeo) is a basal insulin for once-daily administration at any

time of the day, preferably at the same time every day. When needed, people can administer Toujeo up to 3 hours before or after their usual time of administration. It is administered subcutaneously by injection (Toujeo summary of product characteristics).

In adults with type 1 diabetes, Toujeo is used once-daily with meal-time insulin and requires individual dose adjustments. In adults with type 2 diabetes, the recommended daily starting dose is 0.2 units/kg followed by individual dose adjustments.

The potency of Toujeo is stated in units. These units are exclusive to Toujeo and are not the same as IU or the units used to express the potency of other insulin analogues (Toujeo summary of product characteristics). Toujeo is not bioequivalent to Lantus and dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa (MHRA Drug Safety Update April 2015). Dose conversion instructions are given in the Toujeo guidance for healthcare professionals, and are summarised below.

Switch from insulin glargine 100 units/ml to Toujeo

- Switching from insulin glargine 100 units/ml to once-daily Toujeo can be done unit-to-unit based on previous dose.
- A higher Toujeo dose (approximately 10–18%) may be needed to achieve target ranges for plasma glucose levels.

Switch from other basal insulins to Toujeo

- Switching from once-daily basal insulins to once-daily Toujeo can be done unit-to-unit based on previous dose.
- Switching from twice-daily basal insulins to once-daily Toujeo, the recommended initial Toujeo dose is 80% of the total daily dose of basal insulin that is being discontinued.

When switching from a treatment regimen with an intermediate or long-acting insulin product to a regimen with Toujeo, a change of the dose of the basal insulin may be required and the concomitant anti-hyperglycaemic treatment may need to be adjusted.

Switch from Toujeo to insulin glargine 100 units/ml or other basal insulin products

- People who are changing their basal insulin regimen from once-daily Toujeo to a once-daily regimen with insulin glargine 100 units/ml should reduce their dose by 20%.

- Switching from Toujeo to insulin glargine 100 units/ml results in an increased risk of hypoglycaemic events, mainly in the first week after the switch – the dose of insulin glargine 100 units/ml should therefore be reduced.

Close metabolic monitoring is required during any switch and in the initial weeks thereafter.

Toujeo is available in a pack containing 3 pens. Each pen contains 1.5 ml of insulin glargine 300 units/ml solution for injection, equivalent to 450 units. A dose of 1 to 80 units per injection, in steps of 1 unit, can be injected. The dose window shows the number of Toujeo units to be injected. The cost of a pack of 3 pens is £33.13 (excluding VAT; MIMS November 2015).

Evidence review

This evidence summary is based on the 3 main phase 3 studies of Toujeo in adults with type 2 diabetes (EDITION 1, EDITION 2 and EDITION 3). The objective of these studies was to demonstrate that insulin glargine 300 units/ml (Toujeo) is non-inferior to insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction and, based on its pharmacodynamic and pharmacokinetic profiles, is associated with a lower risk of hypoglycaemia.

EDITION 1 was in adults with type 2 diabetes who were using basal and mealtime insulin. In EDITION 2, adults with type 2 diabetes were using oral blood glucose lowering drugs and basal insulin; and in EDITION 3, adults with type 2 diabetes were insulin-naive.

The main phase 3 study of Toujeo in adults with type 1 diabetes (EDITION 4) is reviewed in the evidence summary on type 1 diabetes.

EDITION 1 (Riddle et al. 2014)

- Design: Multicentre, open-label, parallel-group randomised controlled trial (RCT) conducted in 13 countries in North America, Europe and South Africa. There was a 6-month main study period followed by a 6-month comparative safety extension period. Randomisation was centralised and stratified by HbA1c level <8.0% (<64 mmol/mol) and ≥8.0% (≥64 mmol/mol).

- Population: 807 adults (mean age 60 years) with type 2 diabetes who had been using basal insulin (≥42 units/day of either insulin glargine 100 units/ml or NPH insulin) and mealtime insulin (with insulin lispro, aspart or glulisine) with or without metformin for at least 1 year and had an HbA1c level of 7.0% to 10.0% (≥53 to ≤86 mmol/mol). People using other insulins, oral or injected glucose lowering drugs in the last 3 months were excluded. At baseline, the mean duration of diabetes was 16 years, mean HbA1c was 8.15% (65.6 mmol/mol), mean body mass index (BMI) was 36.6 kg/m^2 (standard deviation 6.5), mean basal insulin dose was 0.67 units/kg/day (70 units/day) and 57% were taking metformin.
- Intervention and comparison: participants were randomised 1:1 to once daily injections of insulin glargine 300 units/ml (Toujeo) or insulin glargine 100 units/ml (Lantus) in the evening for 6 months. For people previously using Lantus or once-daily NPH, the starting dose of Toujeo or Lantus was the basal insulin dose used in the 3 days before randomisation. For people taking NPH insulin more than once daily, the dose of Toujeo or Lantus was reduced by approximately 20%. Basal insulin dose was generally adjusted weekly aiming for a pre-breakfast self-measured plasma glucose of 4.4 to 5.6 mmol/litre based on the median of the previous 3 days. Mealtime insulin doses were adjusted at the discretion of the investigator after basal insulin had been optimised. Metformin was continued throughout the study at the baseline dose.

- Outcome: the primary end point was HbA1c change from baseline to month 6 or the last visit on treatment in the modified intention to treat population (all randomised participants who received at least 1 dose of study insulin and had a baseline and 1 or more post-baseline assessments). This was analysed using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) method to handle missing data. The RCT was designed to demonstrate non-inferiority of Toujeo compared with Lantus (with a non-inferiority margin of <0.4% [<4.4 mmol/mol] for the upper bound of the 2-sided 95% confidence interval [CI]). If non-inferiority was demonstrated for HbA1c, superiority could be tested (superiority was demonstrated if the upper bound of the 2-sided 95% CI for the difference was less than 0). The main secondary end point was the percentage of participants with 1 or more confirmed (≤3.9 mmol/L) or severe (requiring assistance) nocturnal hypoglycaemic event between week 9 and month 6. Nocturnal hypoglycaemia was predefined as episodes occurring between midnight and 0559 hours. Other secondary end points included change from baseline in fasting plasma glucose, percentage of participants with HbA1c <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol), change in basal and total daily insulin doses, and change in body weight. Safety assessments included the percentage of participants experiencing hypoglycaemic events and the occurrence of adverse events in the safety population (all randomised participants who received at least 1 dose of study insulin). Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DSTQ).

Table 1 Summary of EDITION 1 (Riddle et al. 2014)

	Insulin glargine 300 units/ml (Toujeo)	**Insulin glargine 100 units/ml (Lantus)**	**Analysis**
Randomised	n=404	n=403	
Efficacy[a]	n=404	n=400	

Primary outcome: mean change in HbA1c from baseline to month 6	−0.83% [−9.1 mmol/mol] from baseline of 8.15% [65.6 mmol/mol]	−0.83% [−9.1 mmol/mol] from baseline of 8.16% [65.7 mmol/mol]	LS mean change difference 0.00% [0.00 mmol/mol], 95% CI −0.11 to 0.11% [−1.2 to 1.2 mmol/mol] Non-inferiority demonstrated[b]
Selected secondary outcomes:			
Participants experiencing at least 1 confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6[c]	36.1% (146/404)	46.0% (184/400)	RR 0.79 (95% CI 0.67 to 0.93), p=0.0045
Participants with HbA1c of less than 7.0% (53 mmol/mol) at month 6	39.6% (155/391)	40.9% (161/394)	No statistical analysis reported
Mean basal insulin dose at 6 months	0.97 units/kg/day (103 units/day) from baseline dose of 0.67 units/kg/day (70 units/day)	0.88 units/kg/day (94 units/day from baseline dose of 0.67 units/kg/day (71 units/day)	LS mean difference 0.09 units/kg/day (95% CI 0.062 to 0.124)
Safety[e]	n=404	n=402	
Mean change in bodyweight at month 6	+0.9 kg	+0.9 kg	No statistical analysis reported
Participants reporting serious treatment emergent adverse events	6.4% (26/404)	5.2% (21/402)	No statistical analysis reported
Participants reporting injection site reactions	2.2% (9/404)	1.5% (6/402)	No statistical analysis reported

Participants with adverse events leading to withdrawal	1.5% (6/404)	1.7% (7/402)	No statistical analysis reported

Abbreviations: CI, confidence interval; LS, least square; p, p value; RR, relative risk; SE, standard error.

[a] Modified intention-to-treat population: all participants who received at least 1 dose of study insulin and had a baseline assessment and at least 1 post-baseline assessment of HbA1c.

[b] Non-inferiority was demonstrated if the upper bound of the 2-sided 95% confidence interval for the mean difference between groups did not exceed 0.40% (4.4 mmol/mol).

[c] A nocturnal hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between midnight and 05:59 hours.

[d] A daytime hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between 06:00 and 23:59 hours.

[e] Safety population: all participants who received at least 1 dose of study insulin.

EDITION 2 (Yki-Jarvinen et al. 2014)

- Design: Multicentre, open-label, parallel-group randomised controlled trial (RCT) conducted in 13 countries in North and South America, Europe and South Africa. There was a 6-month main study period followed by a 6-month comparative safety extension period. Randomisation was centralised and stratified by HbA1c level <8.0% (<64 mmol/mol) and ≥8.0% (≥64 mmol/mol).

- Population: 811 adults (mean age 58 years) with type 2 diabetes who had been using basal insulin (≥42 units/day of either insulin glargine 100 units/ml or NPH insulin) combined with oral blood glucose lowering drugs for at least 6 months and had an HbA1c level of 7.0% to 10.0% (≥53 to ≤86 mmol/mol). People using other insulins (including mealtime insulin), sulfonylureas or new glucose lowering drugs in the last 2 or 3 months were excluded. At baseline, the mean duration of diabetes was 13 years, mean HbA1c was 8.24% (66.6 mmol/mol), mean BMI was 34.8 kg/m^2 (standard deviation 6.4), and mean basal insulin was 0.67 units/kg/day (65 units/day). Most people (94%) were taking metformin at baseline with lower percentages of people taking DPP-4 inhibitors or other oral treatment.

- Intervention and comparison: participants were randomised 1:1 to once daily injections of insulin glargine 300 units/ml (Toujeo) or insulin glargine 100 units/ml (Lantus) in the evening for 6 months. For people previously using Lantus or once-daily NPH, the starting dose of Toujeo or Lantus was the basal insulin dose used in the before randomisation. For people taking NPH more than once daily, the dose of Toujeo or Lantus was reduced by approximately 20%. Basal insulin dose was adjusted weekly aiming for a pre-breakfast self-measured plasma glucose of 4.4 to 5.6 mmol/litre based on the median of the previous 3 days. Oral blood glucose lowering drugs (with the exception of sulfonylureas) were continued at a stable dose. Rescue treatment was allowed at the investigators discretion.

- Outcome: the primary end point was HbA1c change from baseline to month 6 or the last visit on treatment without rescue therapy in the modified intention to treat population (all randomised participants who received at least 1 dose of study insulin and had a baseline and 1 or more post-baseline assessments). This was analysed using an analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) method to handle missing data. The RCT was designed to demonstrate non-inferiority of Toujeo compared with Lantus (with a non-inferiority margin of <0.4% [<4.4 mmol/mol] for the upper bound of the 2-sided 95% confidence interval [CI]). If non-inferiority was demonstrated for HbA1c, superiority could be tested (superiority was demonstrated if the upper bound of the 2-sided 95% CI for the difference was less than 0). The main secondary end point was the percentage of participants with 1 or more confirmed (≤3.9 mmol/L) or severe (requiring assistance) nocturnal hypoglycaemic event between week 9 and month 6. Nocturnal hypoglycaemia was predefined as episodes occurring between midnight and 0559 hours. Other secondary end points included change from baseline in fasting plasma glucose, percentage of participants with HbA1c <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol), change in basal and total daily insulin doses, and change in body weight. Safety assessments included the percentage of participants experiencing hypoglycaemic events and the occurrence of adverse events in the safety population (all randomised participants who received at least 1 dose of study insulin). Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DSTQ).

Table 2 Summary of EDITION 2 (Yki-Jarvinen et al. 2014)

	Insulin glargine 300 units/ml (Toujeo)	**Insulin glargine 100 units/ml (Lantus)**	**Analysis**
Randomised	n=404	n=407	
Efficacy[a]	n=403	n=405	

Primary outcome: mean change in HbA1c from baseline to month 6	−0.57% [−6.2 mmol/mol] from baseline of 8.26% [66.8 mmol/mol]	−0.56% [−6.1 mmol/mol] from baseline of 8.22% [66.3 mmol/mol]	LS mean change difference −0.01% [0.1 mmol/mol], 95% CI −0.14 to 0.12% [−1.5 to 1.3 mmol/mol] Non-inferiority demonstrated[b]
Selected secondary outcomes:			
Participants experiencing at least 1 confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6[c]	21.6% (87/403)	27.9% (113/405)	RR 0.77 (95% CI 0.61 to 0.99), p=0.038
Participants with HbA1c of less than 7.0% (53 mmol/mol) at month 6	30.6% (118/386)	30.4% (119/392)	No statistical analysis reported
Mean basal insulin dose at 6 months	0.92 units/kg/day (91 units/day) from baseline dose of 0.64 units/kg/day)	0.84 units/kg/day (82 units/day) from baseline dose of 0.66 units/kg/day)	LS mean difference 11 units/day (95% CI 8 to 14)
Safety[e]	n=403	n=406	
Mean change in bodyweight at month 6	+0.08 kg	+0.66 kg	p=0.015
Participants reporting serious treatment emergent adverse events	3.7% (15/403)	3.7% (15/406)	No statistical analysis reported
Participants reporting injection site reactions	0.7% (3/403)	2.7% (11/406)	No statistical analysis reported

Participants with adverse events leading to withdrawal	1.5% (6/403)	1.0% (4/406)	No statistical analysis reported

Abbreviations: CI, confidence interval; LS, least square; p, p value; RR, relative risk; SE, standard error.

[a] Modified intention-to-treat population: all participants who received at least 1 dose of study insulin and had a baseline assessment and at least 1 post-baseline assessment of HbA1c.

[b] Non-inferiority was demonstrated if the upper bound of the 2-sided 95% confidence interval for the mean difference between groups did not exceed 0.40% (4.4 mmol/mol).

[c] A nocturnal hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between midnight and 05:59 hours.

[d] A daytime hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between 06:00 and 23:59 hours.

[e] All participants who received at least 1 dose of study insulin.

EDITION 3 (Bolli et al. 2015)

- Design: Multicentre, open-label, parallel-group randomised controlled trial (RCT) conducted in 15 countries in North America, Europe and Japan. There was a 6-month main study period followed by a 6-month comparative safety extension period. Randomisation was centralised and stratified by HbA1c level <8.0% (<64 mmol/mol) and ≥8.0% (≥64 mmol/mol).

- Population: 878 adults (mean age 58 years) with type 2 diabetes who had been using oral blood glucose lowering drugs for at least 6 months (but were insulin-naive) and had an HbA1c level of 7.0% to 11.0% (≥53 to ≤97 mmol/mol). If people were using sulfonylureas or meglitinides these were discontinued at baseline. At baseline, the mean duration of diabetes was 10 years, mean HbA1c was 8.54% (69.8 mmol/mol) and mean BMI was 33.0 kg/m^2 (standard deviation 6.7). Within the 3 months before randomisation, 91% of people had taken metformin, 59% had taken a sulfonylurea and 22% had taken DPP-4 inhibitors.

- Intervention and comparison: participants were randomised 1:1 to once daily injections of insulin glargine 300 units/ml (Toujeo) or insulin glargine 100 units/ml (Lantus) in the evening for 6 months. The starting dose was 0.2 units/kg for both insulins. Basal insulin dose was generally adjusted weekly aiming for a pre-breakfast self-measured plasma glucose of 4.4 to 5.6 mmol/litre based on the median of the previous 3 days. Oral blood glucose lowering drugs (with the exception of sulfonylureas and meglitinides which were stopped) were continued at a stable dose. Rescue treatment was allowed at the investigators discretion.

- Outcome: the primary end point was HbA1c change from baseline to month 6 or the last visit on treatment without rescue therapy in the modified intention to treat population (all randomised participants who received at least 1 dose of study insulin and had a baseline and 1 or more post-baseline assessments). The RCT was designed to demonstrate non-inferiority of Toujeo compared with Lantus (with a non-inferiority margin of <0.4% [<4.4 mmol/mol] for the upper bound of the 2-sided 95% CI). If non-inferiority was demonstrated for HbA1c, superiority could be tested (superiority was demonstrated if the upper bound of the 2-sided 95% CI for the difference was less than 0). The main secondary end point was the percentage of participants with 1 or more confirmed (≤3.9 mmol/L) or severe (requiring assistance) nocturnal hypoglycaemic event between week 9 and month 6. Nocturnal hypoglycaemia was predefined as episodes occurring between midnight and 0559 hours. Other secondary end points included change from baseline in fasting plasma glucose, percentage of participants with HbA1c <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol), change in basal and total daily insulin doses, and change in body weight. Safety assessments included the percentage of participants experiencing hypoglycaemic events and the occurrence of adverse events in the safety population (all randomised participants who received at least 1 dose of study insulin). Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DSTQ). End points were analysed using a mixed model for repeated measurements (MMRM).

Table 3 Summary of EDITION 3 (Bolli et al. 2015)

	Insulin glargine 300 units/ml (Toujeo)	Insulin glargine 100 units/ml (Lantus)	Analysis
Randomised	n=439	n=439	
Efficacy[a]	n=432	n=430	

Primary outcome: mean change in HbA1c from baseline to month 6	−1.42% [−15.5 mmol/mol] from baseline of 8.49% [69.3 mmol/mol]	−1.46% [−16.0 mmol/mol] from baseline of 8.58% [70.3 mmol/mol]	LS mean change difference 0.04% [0.4 mmol/mol], 95% CI −0.09 to 0.17% [−1.0 to 1.9 mmol/mol] Non-inferiority demonstrated[b]
Selected secondary outcomes:			
Participants experiencing at least 1 confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6[c]	15.5% (67/432)	17.4% (75/430)	RR 0.89 (95% CI 0.66 to 1.20) No statistically significant difference
Participants with HbA1c of less than 7.0% (53 mmol/mol) at month 6	43.1% (186/432)	42.1% (181/430)	No statistical analysis reported
Mean basal insulin dose at 6 months	0.62 units/kg/day (59 units/day); people were insulin naive at baseline	0.53 units/kg/day (52 units/day); people were insulin naive at baseline	No statistical analysis reported
Safety[e]	n=435	n=438	
Mean change in bodyweight at month 6	+0.49 kg	+0.71 kg	No statistically significant difference
Participants reporting serious treatment emergent adverse events	6% (24/435)	6% (26/438)	No statistical analysis reported
Participants reporting injection site reactions	4% (17/435)	5% (21/438)	No statistical analysis reported

Participants with adverse events leading to withdrawal	1% (5/435)	1% (5/438)	No statistical analysis reported

Abbreviations: CI, confidence interval; LS, least square; p, p value; RR, relative risk; SE, standard error.

[a] Modified intention-to-treat population: all participants who received at least 1 dose of study insulin and had a baseline assessment and at least 1 post-baseline assessment of HbA1c.

[b] Non-inferiority was demonstrated if the upper bound of the 2-sided 95% confidence interval for the mean difference between groups did not exceed 0.40% (4.4 mmol/mol).

[c] A nocturnal hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between midnight and 05:59 hours.

[d] A daytime hypoglycaemic event was predefined as confirmed (≤3.9 mmol/litre) or severe (requiring assistance) hypoglycaemia occurring between 06:00 and 23:59 hours.

[e] Safety population: all participants who received at least 1 dose of study insulin.

Clinical effectiveness

In EDITION 1 (n=807), EDITION 2 (n=811) and EDITION 3 (n=878), once-daily insulin glargine 300 units/ml (Toujeo) was non-inferior to once-daily insulin glargine 100 units/ml (Lantus) in adults with type 2 diabetes. A similar reduction in HbA1c from baseline to month 6 was seen in both treatment groups in each study. In EDITION 1 the difference between groups was 0.00% [0.00 mmol/mol], 95% confidence interval [CI] −0.11 to 0.11% [−1.2 to 1.2 mmol/mol] in people who were already using basal and mealtime insulin at baseline. In EDITION 2 the difference was −0.01% [0.1 mmol/mol], 95% CI −0.14 to 0.12% [−1.5 to 1.3 mmol/mol] in people who were using oral blood glucose lowering drugs and basal insulin at baseline. In EDITION 3, in people who were insulin-naive at baseline, the difference was 0.04% [0.4 mmol/mol], 95% CI −0.09 to 0.17% [−1.0 to 1.9 mmol/mol]. In a post-hoc patient-level meta-analysis of EDITION 1, EDITION 2 and EDITION 3 (n=2496; Ritzel et al 2015) the reduction in HbA1c from baseline to month 6 was 1.02% [11.1 mmol/mol] in both groups (difference 0.00%, 95% CI −0.08 to 0.07% [0.00 mmol/mol, 95% CI −0.9 to 0.8 mmol/mol]). 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 (see tables 1, 2 and 3 for details).

The main secondary end point in all 3 RCTs was the percentage of participants experiencing at least 1 confirmed or severe nocturnal hypoglycaemic event between week 9 and month 6. This was statistically significantly lower with Toujeo compared with Lantus in EDITION 1 and EDITION 2, but not in EDITION 3. In EDITION 1 the percentages were 36% with Toujeo and 46% with Lantus (relative risk [RR] 0.79; 95% CI 0.67 to 0.93, p=0.0045); in EDITION 2 they were 22% with Toujeo and 28% with Lantus (RR 0.77; 95% CI 0.61 to 0.99, p=0.038); and in EDITION 3 they were 16% with Toujeo and 17% with Lantus (RR 0.89; 95% CI 0.66 to 1.20, p=0.4536). Severe nocturnal hypoglycaemic events were rare in all 3 RCTs and too few for meaningful analysis.

In the post-hoc meta-analysis of EDITION 1, EDITION 2 and EDITION 3 (Ritzel et al 2015), the annualised rates of confirmed or severe nocturnal events over the 6-month study period were 31% lower with Toujeo compared with Lantus (2.10 events per participant-year with Toujeo and 3.06 events per participant-year with Lantus; RR 0.69, 95% CI 0.57 to 0.84, p=0.0002). This is a reduction of approximately 1 confirmed or severe nocturnal event per person per year, which is of debatable clinical significance. Severe hypoglycaemia was rare in both groups in all 3 RCTs. In the post-hoc meta-analysis, the percentage of participants with at least 1 severe event at any time of day was 2.3% with Toujeo and 2.6% with Lantus; not statistically significantly different (RR 0.85, 95% CI 0.52 to 1.39). There were 0.11 severe events per participant-year in both groups (Ritzel et al 2015).

In all 3 RCTs, more hypoglycaemic events occurred during the day rather than at night. For hypoglycaemia at any time of day or night, the relative risk of at least 1 confirmed or severe hypoglycaemic event per participant from week 9 to month 6 was not statistically significantly different with Toujeo compared with Lantus in any of the trials (EDITION 1: RR 0.96, 95% CI 0.89 to 1.04; EDITION 2: RR 0.91, 95% CI 0.82 to 1.02; EDITION 3: RR 0.86, 95% CI 0.74 to 1.00). However, in the post-hoc patient-level meta-analysis of EDITION 1, 2 and 3 (Ritzel et al 2015), the annualised rates of confirmed or severe hypoglycaemia at any time of day or night over the 6-month study period were 14% lower with Toujeo compared with Lantus (15.22 events per participant-year with Toujeo and 17.73 events per participant-year with Lantus; RR 0.86, 95% CI 0.77 to 0.97, p=0.0116). When analysed by study period, the meta-analysis also showed that reductions in hypoglycaemic events with Toujeo compared with Lantus were apparent during the first 8 weeks of treatment as well as during the maintenance period of week 9 to month 6.At 6 months the basal insulin dose

was higher with Toujeo than with Lantus in all 3 RCTs. In EDITION 1, the Toujeo dose at 6 months was 0.97 units/kg/day and the Lantus dose was 0.88 units/kg/day; 10% higher with Toujeo. In EDITION 2, the Toujeo dose at 6 months was 0.92 units/kg/day and the Lantus dose was 0.84 units/kg/day; 10% higher with Toujeo. In EDITION 3, the Toujeo dose was 0.62 units/kg/day and the Lantus dose was 0.53 units/kg/day; 17% higher with Toujeo. In the meta-analysis (Ritzel et al 2015), the mean basal insulin dose at month 6 was 0.85 units/kg/day with Toujeo and 0.76 units/kg/day with Lantus, a 12% higher dose with Toujeo.

There were no differences in any participant-reported outcomes between the Toujeo and Lantus groups.

Twelve-month results from EDITION 1 (Riddle et al 2015) in adults with type 2 diabetes using basal and mealtime insulin and EDITION 2 (Yki-Järvinen H et al. 2015) in adults with type 2 diabetes using oral blood glucose lowering drugs and basal insulin have now been published. In both trials, glycaemic control was sustained with Toujeo, as were the benefits of Toujeo over Lantus in the percentage of people experiencing nocturnal hypoglycaemia.

Safety and tolerability

In a post-hoc patient-level meta-analysis of EDITION 1, EDITION 2 and EDITION 3 (n=2496; Ritzel et al 2015), no differences in the safety profile of Toujeo and Lantus were seen. Treatment-emergent adverse events were reported by 712 (57.3%) people in the Toujeo group and 669 (53.7%) people in the Lantus group, with 65 (5.2%) and 62 (5.0%) people reporting serious events respectively. Similar numbers of participants reported injection site reactions (2.4% with Toujeo and 3.1% with Lantus), and similar numbers withdrew because of adverse events (1.4% with Toujeo and 1.3% with Lantus). Deaths occurred in 4 people in the Toujeo group and 3 people in the Lantus group, but none of these were considered to be related to study treatment. Body weight increased with both Toujeo and Lantus, but at month 6 the mean increase was smaller with Toujeo (0.51 kg) than with Lantus (0.79 kg; p=0.039). In EDITION 1, body weight increased by 0.9 kg in both groups at month 6. In EDITION 2, the weight gain at 6 months was 0.08 kg with Toujeo and 0.66 kg with Lantus (p=0.015), and in EDITION 3 it was 0.49 kg with Toujeo and 0.71 kg with Lantus (no statistically significant difference). Further safety data from the individual RCTs are given in tables 1, 2 and 3.

In the European public assessment report (EPAR) for Toujeo, all people from phase 1, 2 or 3 studies who were randomised and received at least 1 dose of Toujeo were evaluated for

safety. This includes people with type 1 and type 2 diabetes, and some people who were treated for at least 1 year. Across all studies (n=1546 for Toujeo and n=1550 for Lantus) the number and overall pattern of adverse events were comparable between treatment groups. The most frequent adverse events were nasopharyngitis (8.2% with Toujeo, 6.8% with Lantus) and upper respiratory tract infection (6.5% with Toujeo, 5.8% with Lantus). Most of the adverse events were mild to moderate in intensity. Events of severe intensity were reported in 5.1% of the Toujeo group and 4.1% of the Lantus group, with the most frequent in both groups being hypoglycaemia (0.5% with Toujeo and 0.8% with Lantus).

The EPAR reports that the safety profile of Toujeo is largely similar to that of Lantus and no additional safety signals were detected for Toujeo with regard to injection site reactions, hypersensitivity reactions, malignancy, hepatic safety or cardiovascular safety. However, the Toujeo clinical development programme was not designed specifically to address cardiovascular risk because this has been established for Lantus. The percentage of people with any major cardiovascular event was low and comparable with Toujeo and Lantus.

An important risk with high-strength insulin glargine 300 units/ml (Toujeo) is possible medication errors with other insulins of lower strengths. The European Medicines Agency has recently consulted on guidance to minimise the potential risk of medication errors associated with the availability of high-strength insulins and fixed combinations of insulin with another non-insulin injectable blood glucose lowering agent (MHRA Drug Safety Update April 2015).

The MHRA advice in Drug Safety Update April 2015 is that before starting treatment with a high strength, fixed combination or biosimilar insulin product, healthcare professionals should:

- consult the summary of product characteristics and any educational material
- ensure that patients read and understand the patient leaflet and any patient education material
- ensure that patients receive appropriate training on the correct use of the product
- give patients a patient booklet and Insulin Passport (or safety card)
- warn patients only to use insulin as they have been trained because using it any other way may result in a dangerous overdose or underdose.

Patients should monitor glucose levels closely after starting a new treatment and in the following weeks. They may need to adjust doses and timing of concurrent rapid-acting or short-acting insulin products and other antidiabetic treatments.

The Toujeo guidance for healthcare professionals recommends that the trade name and concentration (Toujeo SoloStar 300 units/ml) must be written on each prescription for Toujeo, along with the recommended dose in units. The dose window of the Toujeo SoloStar pen shows the number of units of Toujeo to be injected. The guidance advises patients that Toujeo is not bioequivalent and not interchangeable with any other basal insulin including insulin glargine 100 units/ml, without individualised dose adjustment. Blood glucose monitoring is needed during the switch and the initial weeks thereafter. Toujeo guidance for patients and carers is also available.

Evidence strengths and limitations

There are several limitations with EDITION 1, EDITION 2 and EDITION 3, which the authors discuss. The trials were all open-label because Toujeo and Lantus are different pen injectors. This could lead to technology bias in favour of the new insulin or familiarity bias in favour of the comparator. There is also a concern over possible confounding by adjustment of the prandial insulin dose in EDITION 1

In EDITION 1 and EDITION 2, participants were required to have current basal insulin treatment of 42 units/day or more, and these results may not be generalisable to people with lower basal insulin requirements. Although EDITION 3 was conducted in people who were insulin-naive at baseline.

More hypoglycaemia events in EDITION 1, 2 and 3 occurred during the day rather than at night. These could have been related to prandial rather than basal insulin in EDITION 1. However, the prolonged action of Toujeo may have caused a relative shift of long-acting insulin action from night to day. The EPAR states that for Toujeo, nocturnal hypoglycaemia events were somewhat lower and daytime hypoglycaemia events were higher in some categories, especially in combination with mealtime insulin. However, most differences were small and mealtime insulin in combination with basal insulin contributes significantly to the increase in the number of daytime hypoglycaemia events.

The baseline characteristics were largely similar between groups in EDITION 1, 2 and 3. In all 3 RCTs, mean BMI was high (in EDITION 1 it was 36.6 kg/m^2, in EDITION 2 it was 34.8 kg/m^2 and in EDITION 3 it was 33.0 kg/m^2) and results may not be generalisable to

people with a lower BMI. Discontinuation of treatment insulin before 6 months was 7% in the Toujeo group and 8% in the Lantus group in EDITION 1, 9% in both groups in EDITION 2, and 14% in the Toujeo group and 17% in the Lantus group in EDITION 3.

EDITION 1, 2 and 3 were designed to demonstrate non-inferiority of Toujeo to Lantus using a pre-specified non-inferiority margin of 0.4% [4.4 mmol/mol]. The EPAR states that although a margin of 0.4% is considered too wide, the actual upper limits (0.11%, 0.12% and 0.17%) were well below the more desired margin of 0.3%. End points were analysed in the modified intention to treat population using an ANCOVA model or a mixed model for repeated measurements (MMRM) approach. There are no data reported in the published papers or the EPAR for the per-protocol population, which would be usual for a non-inferiority study.

The primary end point of EDITION 1, 2 and 3, which were conducted in 2496 adults with type 2 diabetes, was an HbA1c end point at 6 months. Extension studies to 12 months have been completed, and published for EDITION 1 and EDITION 2. There are very limited patient-oriented outcome data on macrovascular or microvascular outcomes with Toujeo, or on the long-term safety of this particular formulation. However, the Toujeo summary of product characteristics includes reference to long-term studies with insulin glargine 100 units/ml (Lantus), such as the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial.

Context

Alternative treatments

Basal insulin supply for adults with type 2 diabetes can be provided by:

- NPH (isophane) insulin (for example, Insulatard, Humulin I or Insuman Basal) **or**
- Long-acting insulin analogues: insulin glargine (Lantus, the biosimilar Abasaglar or high-strength Toujeo), insulin detemir (Levemir) or insulin degludec (Tresiba).

Costs of alternative treatments

	5×3 ml cartridge	5×3 ml pre-filled pen

Insulatard NPH (isophane) insulin 100 units/ml solution	£22.90	£20.40
Humulin I NPH (isophane) insulin 100 units/ml solution	£19.08	£21.70
Insuman Basal NPH (isophane) insulin 100 units/ml solution	£17.50	£19.80
Lantus insulin glargine 100 units/ml solution	£41.50	£41.50
Abasaglar biosimilar insulin glargine 100 units/ml solution	£35.28	£35.28
Toujeo high-strength insulin glargine 300 units/ml solution	-	3×1.5 ml pre-filled pen, £33.13[a]
Levemir insulin detemir 100 units/ml solution	£42.00	£42.00 or £44.85
Tresiba insulin degludec 100 units/ml solution	£72.00	£72.00
Tresiba insulin degludec 200 units/ml solution	-	3×3 ml pre-filled pen, £86.40
Costs are excluding VAT; taken from MIMS (November 2015). [a] The manufacturer has stated that Toujeo has been priced at a level to match the daily cost of Lantus on the basis of average insulin glargine usage in the EDITION trials (personal communication September 2015).		

Toujeo (insulin glargine 300 units/ml) is the third insulin to be approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. Insulin degludec (Tresiba) and insulin lispro (Humalog) are already available as 200 units/ml strength.

The cost of Toujeo and other basal insulins will depend on the preparation chosen and the insulin dosage used.

Estimated impact for the NHS

Likely place in therapy

Toujeo is a high-strength insulin glargine product containing 300 units/ml solution for injection in a pre-filled pen (Toujeo Summary of Product Characteristics). It is a basal insulin for once-daily use for the treatment of diabetes mellitus in adults. In people with type 2 diabetes mellitus, it can be given together with other anti-hyperglycaemic medicinal products.

High strength insulin products have been developed for people with large daily insulin requirements to reduce the number and volume of injections (MHRA Drug Safety Update April 2015). Specialists involved in the production of this publication have suggested that certain people with type 2 diabetes who are insulin resistant use very high basal insulin doses. Due to the higher concentration of insulin, the volume to be injected is smaller, which may be less painful for people injecting large volumes. However, there was no information on injection site pain with Toujeo compared with Lantus in the Toujeo study programme. In the main phase 3 studies of Toujeo in type 2 diabetes, similar numbers of people reported injection site reactions in both groups (2.4% with Toujeo and 3.1% with Lantus).

The EPAR states that the reduction in injection volume could be of importance especially for people who require large amounts of insulin. However, the limitation to 80 units per injection may mean that some people still need more than 1 injection, to some extent negating the most obvious advantage of Toujeo (European public assessment report [EPAR] for Toujeo). Injection volumes aren't given in EDITION 1, 2 or 3. However, based on the mean insulin dose at 6 months (Ritzel et al 2015), for a 90 kg adult, these are calculated to be 77 units in 0.3 ml for Toujeo and 68 units in 0.8 ml for Lantus. Specialists involved in the production of this evidence summary have suggested that single injections containing up to 60 units of standard strength insulin (0.6 ml for Lantus) are usually well tolerated; above this more than 1 injection is advised.

The phase 3 studies of Toujeo in adults with type 2 diabetes (EDITION 1, EDITION 2 and EDITION 3) were designed to demonstrate that insulin glargine 300 units/ml (Toujeo) is

non-inferior to insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction and, based on its pharmacodynamic and pharmacokinetic profiles, is associated with a lower risk of hypoglycaemia. All the EDITION studies in people with type 2 diabetes showed that Toujeo had similar efficacy to Lantus, and 2 of the 3 found that there was a statistically significant reduction in confirmed or severe nocturnal hypoglycaemia with Toujeo compared with Lantus. In a post-hoc meta-analysis (Ritzel et al 2015), the absolute reduction in these nocturnal hypoglycaemic events was about 1 event per person per year (2.10 events per participant-year with Toujeo and 3.06 events per participant-year with Lantus; RR 0.69, 95% CI 0.57 to 0.84, p=0.0002). Severe hypoglycaemic events at any time of day were rare and not statistically significantly different between groups. The EPAR states that the more gradual glucose lowering effect of Toujeo compared with Lantus did not translate into important advantages, and the higher use of basal insulin may be a disadvantage. In order to obtain a similar effect on HbA1c, on average 12% higher doses of Toujeo than Lantus were used in people with type 2 diabetes.

Toujeo (insulin glargine 300 units/ml) is the third insulin to be approved in Europe at a higher strength than the European Union-wide standard of 100 units/ml. The European Medicines Agency has recently consulted on guidance to minimise the potential risk of medication errors associated with the availability of these high-strength insulins (MHRA Drug Safety Update April 2015).

Toujeo is not simply interchangeable with other long-acting insulins, including insulin glargine 100 units/ml. When switching between Toujeo and other basal insulins, different doses may be needed to achieve target ranges for plasma glucose levels, giving rise to a potential risk of medication error. This risk is addressed in advice given in the summary of product characteristics, and educational material for healthcare professionals and patients has been produced as an additional risk minimisation measure.

The updated NICE guideline on type 2 diabetes recommends that when insulin therapy is necessary, it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. Insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see the guideline for details). There are several insulin glargine products available including Lantus, the biosimilar Abasaglar or high-strength Toujeo).

Estimated usage

The manufacturer estimates that the uptake of insulin glargine 300 units/ml (Toujeo) over

the next 5 years for England will be as follows: 2015 (734 people), 2016 (9994 people), 2017 (27,900 people), 2018 (65,386 people), 2019 (80,948 people) and 2020 (90,581 people)

Relevance to NICE guidance programmes

NICE has issued a guideline on type 2 diabetes in adults: management.

References

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Paula Chattington: no relevant interests declared.

Dr Sutapa Ray: spoken at and attended meetings organised or sponsored by pharmaceutical companies.

Dr Vinod Patel: occasional lectures and educational events for all major pharmaceutical companies in the field of diabetes. Conference travel on average once or twice a year and occasional advisory board work.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

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