Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo)

Evidence summary
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nice.org.uk/guidance/esnm62

Key points from the evidence

The content of this evidence summary was up-to-date in October 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 large daily insulin requirements to reduce the number and volume of injections. In 1 randomised controlled trial (RCT) in 549 people with type 1 diabetes, Toujeo had similar efficacy to insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction, but the basal insulin dose used was higher with Toujeo than with Lantus. There was no benefit of Toujeo over Lantus in terms of reduced hypoglycaemic events. 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.

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

- Once-daily Toujeo was non-inferior to once-daily Lantus in HbA1c reduction from baseline to month 6 (difference between groups 0.04% [0.4 mmol/mol], 95% confidence interval [CI] −0.10 to 0.19% [−1.1 to 2.1 mmol/mol]) in people with type 1 diabetes (1 RCT, n=549).

- Hypoglycaemia (confirmed or severe, nocturnal, or severe) did not differ between Toujeo and Lantus at 6 months in people with type 1 diabetes (1 RCT, n=549).

- At 6 months the basal insulin dose was approximately 18% higher with Toujeo than with Lantus (1 RCT, n=549).

Safety

- 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 common serious adverse event in people with type 1 diabetes is hypoglycaemia (European public assessment report [EPAR] for Toujeo).

- In 1 RCT (n=549), similar numbers of participants reported injection site reactions with Toujeo (2.2%) and Lantus (1.5%), and similar numbers withdrew because of adverse events (1.1% in both groups).
### Patient factors

- 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 but can be up to 3 hours before or after usual time.

- Body weight increased less with Toujeo than with Lantus (mean increase at 6 months 0.5 kg compared with 1.0 kg; p=0.037; 1 RCT, n=549).

- 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.

### Resource implications

- 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, September 2015).

### Introduction and current guidance

Type 1 diabetes is a long-term hormonal deficiency disorder treated with insulin replacement therapy. This is supported by active management of other cardiovascular risk factors, such as hypertension and high circulating lipids.

The updated NICE guideline on type 1 diabetes in adults: diagnosis and management recommends multiple daily injection basal–bolus insulin regimens as the insulin injection regimen of choice for all adults with type 1 diabetes. Twice-daily insulin detemir is recommended as the preferred basal insulin therapy; with other basal insulin regimens options in certain circumstances (see the guideline for more details).

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 type 1 diabetes mellitus, it must be combined with short or rapid-acting insulin to cover mealtime insulin requirements and requires individual dose adjustments.

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, September 2015).

Full text of Product overview.

Evidence review

This evidence summary is based on the main phase 3 study of Toujeo in people with type 1 diabetes (EDITION 4). This RCT was designed to demonstrate non-inferiority of insulin glargine 300 units/ml (Toujeo) with insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction in people with type 1 diabetes. The main phase 3 studies of Toujeo in people with type 2 diabetes will be reviewed in the evidence summary on Toujeo for type 2 diabetes (which will be published after the NICE guideline on type 2 diabetes is updated).

- In EDITION 4 (n=549), once-daily Toujeo was non-inferior to once-daily Lantus. A similar reduction in HbA1c from baseline to month 6 was seen in both treatment groups, with a difference between groups of 0.04% (0.4 mmol/mol), 95% CI −0.10 to 0.19% (−1.1 to 2.1 mmol/mol). This was below the pre-specified non-inferiority margin of 0.4%.

- A similar proportion of participants in each treatment group achieved HbA1c below 7.0% (53 mmol/mol) at month 6; 16.8% with Toujeo and 15.0% with Lantus (no statistical analysis reported).
Rates of hypoglycaemia did not differ between treatment groups at 6 months. In the Toujeo group 93.1% of participants had 1 or more confirmed or severe hypoglycaemic event over 6 months compared with 93.5% of the Lantus group (relative risk [RR] 1.00; 95% CI 0.95 to 1.04). Nocturnal confirmed or severe hypoglycaemic events occurred in 68.6% of the Toujeo group and 70.2% of the Lantus group over 6 months (RR 0.98; 95% CI 0.88 to 1.09); and severe hypoglycaemic events in 6.6% of the Toujeo group and 9.5% of the Lantus group (RR 0.71; 95% CI 0.41 to 1.24).

At 6 months the basal insulin dose was approximately 18% higher with Toujeo (0.47 units/kg/day) than with Lantus (0.40 units/kg/day).

In EDITION 4, 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 (0.5 kg compared with 1.0 kg; p=0.037).

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. Overall, serious adverse events were reported by 5.4% of people in both Toujeo and Lantus groups; most commonly hypoglycaemia in people with type 1 diabetes.

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 4 trial (n=549) was HbA1c at 6 months. An extension study to 12 months has been completed, but not yet published. 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 1 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.

**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).

In the main phase 3 study in people with type 1 diabetes (EDITION 4), Toujeo had similar efficacy to Lantus in terms of HbA1c reduction, with no difference in the risk of hypoglycaemia. The EPAR states that in people with type 1 diabetes the only advantage is the reduction in injection volume. However, specialists involved in the production of this evidence summary have suggested that large basal insulin requirements tend to be seen more in people with type 2 diabetes rather than type 1; and in EDITION 4 the mean injection volume at 6 months was calculated to be 0.1 ml (35 units) with Toujeo and 0.3 ml (30 units) with Lantus for a 75 kg adult. The EPAR states that the more gradual glucose lowering effect of Toujeo compared with Lantus did not translate into important advantages in people with type 1 diabetes, and the higher use of basal insulin may be a disadvantage. In order to obtain a similar effect on HbA1c, 18% higher doses of Toujeo than Lantus were needed in EDITION 4.

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 1 diabetes in adults: diagnosis and management recommends twice-daily insulin detemir as the preferred basal insulin therapy. Other basal insulin regimens, including once-daily insulin glargine can also be considered in certain circumstances. When choosing an alternative insulin regimen, the guideline recommends that the person’s preferences and acquisition cost should be taken into account, and that people should have access to the insulin injection delivery device they find allows them optimal wellbeing. Toujeo was not considered specifically in the guideline because it was not available when the guideline was produced.

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 1 diabetes is a long-term hormonal deficiency disorder treated with insulin replacement therapy. This is supported by active management of other cardiovascular risk factors, such as hypertension and high circulating lipids. Over years, type 1 diabetes causes tissue damage which, if not detected and managed early, can result in disability: blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death. The risk of all of these complications is greatly reduced by treatment that keeps circulating glucose levels to as near normal as possible, reducing tissue damage. Modern insulin replacement therapy for type 1 diabetes aims to recreate normal fluctuations in circulating insulin concentrations.

The updated NICE guideline on type 1 diabetes in adults: diagnosis and management recommends that all adults with type 1 diabetes should be offered a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. DAFNE provides people with the skills necessary to estimate the carbohydrate in each meal and to inject the right
dose of insulin. The guideline recommends that adults with type 1 diabetes should be supported to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. HbA1c targets should be individualised taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. Aiming for the target should not be accompanied by problematic hypoglycaemia.

Multiple daily injection basal–bolus insulin regimens are recommended in the guideline as the insulin injection regimen of choice for all adults with type 1 diabetes. Twice-daily insulin detemir is recommended as the preferred basal insulin therapy. An existing insulin regimen being used by the person can be considered as an alternative if that is achieving their agreed targets. Once-daily insulin glargine or insulin detemir can also be considered if twice-daily basal insulin injections are not acceptable, as can once-daily insulin glargine if insulin detemir is not tolerated. Other basal insulin regimens should only be considered if these regimens do not deliver agreed targets. When choosing an alternative insulin regimen, the person's preferences and acquisition cost should be taken into account. The guideline also recommends that adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. The high-strength insulin glargine product, Toujeo, was not considered specifically in this guideline because it was not available when the guideline was produced.

**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](https://www.nice.org.uk/)). 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 (Lantus) 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](https://www.nice.org.uk/)).

Toujeo is not bioequivalent to Lantus and dose adjustment is needed when people are switched from Lantus or other basal insulins to Toujeo or vice versa ([MHRA Drug Safety Update April 2015](https://www.nice.org.uk/)).
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 (Toujeo summary of product characteristics). This evidence summary covers the use of Toujeo in adults with type 1 diabetes. Another evidence summary covers its use in adults with type 2 diabetes (this will be published after the NICE guideline on type 2 diabetes is updated).

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 September 2015).

Evidence review

This evidence summary is based on the main phase 3 study of Toujeo in people with type 1 diabetes
(EDITION 4). The objective of this study 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 studies of Toujeo in people with type 2 diabetes are reviewed in
the evidence summary on type 2 diabetes (which will be published after the NICE guideline on
type 2 diabetes is updated).

EDITION 4 (Home et al. 2015)

- Design: multicentre, open-label, 4-arm, parallel-group randomised controlled trial (RCT)
  conduced in 124 centres across 12 countries (Europe, USA, Canada and Japan). There was a
  6-month main study period followed by a 6-month extension period. The results from the
  extension period have not yet been published.
Population: 846 adults were screened and 549 adults (mean age 47 years, mean body mass index 27.6 kg/m²) were randomised. Included adults had type 1 diabetes for more than 1 year (mean duration 21 years) and were on basal insulin in combination with a mealtime insulin analogue for at least 3 months. Exclusion criteria included HbA1c less than 7.0% (53 mmol/mol) and more than 10.0% (86 mmol/mol), less than 1 year on a basal plus mealtime insulin regimen, unstable insulin dose, use of other mealtime premix insulin or other glucose-lowering medication within 3 months, and pump therapy with 6 months. Mean baseline HbA1c was 8.1% (65 mmol/mol). Most people transferred from insulin glargine 100 units/ml once daily.

Intervention and comparison: participants were centrally randomised (1:1:1:1) to once-daily insulin glargine 300 units/ml (Toujeo) or insulin glargine 100 units/ml (Lantus) injected morning (between pre-breakfast and pre-lunch) or evening (at the evening meal until bedtime), while continuing mealtime insulin. Randomisation was stratified by HbA1c less than 8.0% (64 mmol/mol) and 8.0% (64 mmol/mol) or above. Both basal insulins were titrated to a pre-breakfast self-measured plasma glucose of 80–130 mg/dL (4.4–7.2 mmol/litre). Dose adjustments of basal insulin (between 1.5 and 4.5 units for insulin glargine 300 units/ml, and 1.0 and 4.0 units for insulin glargine 100 units/ml) were made weekly (no more than every 3 to 4 days). Mealtime insulin continued with a target of less than 160 mg/dL (8.9 mmol/litre) for 2-hour postprandial plasma glucose, adjusted at investigator discretion.

Outcomes: the primary efficacy end point was the overall change in HbA1c from baseline to month 6, regardless of injection time, in the modified intention to treat population. This population was defined as all randomised participants who received 1 or more doses of study insulin and had a baseline and 1 or more post baseline assessments of HbA1c. Secondary end points included the percentage of participants with HbA1c below 7% (53 mmol/mol) at month 6, change in pre-injection self-measured plasma glucose, fasting plasma glucose and daily insulin doses. Primary and secondary end points were also analysed by injection time. The percentage of participants experiencing at least 1 hypoglycaemic event was assessed. A hypoglycaemic event was predefined as confirmed or severe hypoglycaemia (all severe and all documented [plasma glucose ≤70 mg/dL or 3.9 mmol/litre] symptomatic and asymptomatic hypoglycaemia; where severe is defined as hypoglycaemia requiring assistance). Nocturnal hypoglycaemia was predefined as episodes occurring between midnight and 0559 hours. Adverse events were systematically recorded at each visit as was bodyweight. Hypoglycaemia, adverse events and bodyweight were analysed in the safety population. This was defined as all participants randomised and exposed to at least 1 dose of study insulin. Participant reported outcomes included satisfaction with treatment and perception of occurrence of hypoglycaemia and hyperglycaemia, assessed with the Diabetes Treatment Satisfaction Questionnaire (DTSQ); health-related quality of life, assessed with the EQ-5D; and behaviours and worries related to hypoglycaemia, assessed with the Hypoglycemia Fear Survey (HFS II).
The RCT was designed to demonstrate non-inferiority (with a margin of 0.40% [4.4 mmol/mol]) of insulin glargine 300 units/ml (Toujeo) with insulin glargine 100 units/ml (Lantus). Superiority of insulin glargine 300 units/ml could be tested if non-inferiority was established. Endpoints were analysed using a mixed model for repeated measurements (MMRM).

**Table 1 Summary of EDITION 4 (Home et al. 2015)**

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine 300 units/ml (Toujeo)</th>
<th>Insulin glargine 100 units/ml (Lantus)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>n=274</td>
<td>n=275</td>
<td></td>
</tr>
<tr>
<td>Efficacy\textsuperscript{a}</td>
<td>n=273</td>
<td>n=273</td>
<td></td>
</tr>
<tr>
<td>Primary outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean change in HbA1c from baseline to month 6</td>
<td>−0.42% [−4.6 mmol/mol] from baseline of 8.13% [65.3 mmol/mol]</td>
<td>−0.44% [−4.8 mmol/mol] from baseline of 8.12% [65.2 mmol/mol]</td>
<td>LS mean change difference 0.04% [0.4 mmol/mol], 95% CI −0.10 to 0.19% [−1.1 to 2.1 mmol/mol] Non-inferiority demonstrated\textsuperscript{b}</td>
</tr>
<tr>
<td>Selected secondary outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with HbA1c of less than 7.0% (53 mmol/mol) at month 6</td>
<td>16.8% (46/273)</td>
<td>15.0% (41/273)</td>
<td>No statistical analysis reported</td>
</tr>
<tr>
<td>Mean basal insulin dose at 6 months</td>
<td>0.47 units/kg/day (baseline dose 0.38 units/kg/day)</td>
<td>0.40 units/kg/day (baseline dose 0.37 units/kg/day)</td>
<td>No statistical analysis reported</td>
</tr>
<tr>
<td>Safety\textsuperscript{c}</td>
<td>n=274</td>
<td>n=275</td>
<td></td>
</tr>
<tr>
<td>Participants experiencing at least 1 hypoglycaemic event over 6 months\textsuperscript{d}</td>
<td>93.1% (255/274) 78.4 events/ person-year</td>
<td>93.5% (257/275) 72.5 events/ person-year</td>
<td>RR 1.00 (95% CI 0.95 to 1.04)</td>
</tr>
<tr>
<td>Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>RR</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
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<tr>
<td>Participants experiencing at least 1 nocturnal hypoglycaemic event over 6 months</td>
<td>68.6% (188/274)</td>
<td>70.2% (193/275)</td>
<td>0.98 (95% CI 0.88 to 1.09)</td>
</tr>
<tr>
<td>Participants experiencing at least 1 severe hypoglycaemic event over 6 months</td>
<td>6.6% (18/274)</td>
<td>9.5% (26/275)</td>
<td>0.71 (95% CI 0.41 to 1.24)</td>
</tr>
<tr>
<td>Change in bodyweight at month 6</td>
<td>+0.5 (SE 3.3) kg</td>
<td>+1.0 (SE 3.2) kg</td>
<td>Difference −0.6 kg (95% CI −1.1 to −0.03), p=0.037</td>
</tr>
<tr>
<td>Participants reporting any treatment emergent adverse event</td>
<td>61% (167/274)</td>
<td>58% (160/275)</td>
<td>No statistical analysis reported</td>
</tr>
<tr>
<td>Participants reporting serious treatment emergent adverse events</td>
<td>6.2% (17/274)</td>
<td>8.0% (22/275)</td>
<td>No statistical analysis reported</td>
</tr>
<tr>
<td>Participants reporting injection site reactions</td>
<td>2.2% (6/274)</td>
<td>1.5% (4/275)</td>
<td>No statistical analysis reported</td>
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<tr>
<td>Participants with adverse events leading to withdrawal</td>
<td>1.1% (3/274)</td>
<td>1.1% (3/275)</td>
<td>No statistical analysis reported</td>
</tr>
</tbody>
</table>
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%.
c All participants who received at least 1 dose of study insulin.
d A hypoglycaemic event was predefined as confirmed or severe hypoglycaemia (all severe and all documented [glucose ≤70 mg/dL or 3.9 mol/litre] symptomatic and asymptomatic hypoglycaemia).
e A nocturnal hypoglycaemic event was predefined as confirmed or severe hypoglycaemia (all severe and all documented [glucose ≤70 mg/dL or 3.9 mol/litre] symptomatic and asymptomatic hypoglycaemia) occurring between midnight and 0559 hours.
f Hypoglycaemia requiring assistance.

Clinical effectiveness

In EDITION 4 (n=549), once-daily insulin glargine 300 units/ml (Toujeo) was non-inferior to once-daily insulin glargine 100 units/ml (Lantus) in people with type 1 diabetes. A similar reduction in HbA1c from baseline to month 6 was seen in both overall (morning and evening use) treatment groups, with a difference between groups of 0.04% (0.4 mmol/mol), 95% confidence interval [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%. Toujeo was also non-inferior to Lantus when morning or evening use was analysed separately, although the populations were smaller and the confidence intervals were wider. A similar proportion of participants in each overall treatment group achieved HbA1c below 7.0% (53 mmol/mol) at month 6; 16.8% with Toujeo and 15.0% with Lantus (no statistical analysis reported).

Rates of hypoglycaemia did not differ between once-daily insulin glargine 300 units/ml (Toujeo) and once-daily insulin glargine 100 units/ml (Lantus) over 6 months. In the Toujeo group 93.1% of participants had 1 or more confirmed or severe hypoglycaemic event over 6 months compared with 93.5% of the Lantus group (relative risk [RR] 1.00; 95% CI 0.95 to 1.04). Nocturnal confirmed or severe hypoglycaemic events occurred in 68.6% of the Toujeo group and 70.2% of the Lantus group over 6 months (RR 0.98; 95% CI 0.88 to 1.09); and severe hypoglycaemic events in 6.6% of the Toujeo group and 9.5% of the Lantus group (RR 0.71; 95% CI 0.41 to 1.24). See table 1 for details. When analysed by morning or evening use, hypoglycaemia with Toujeo did not differ by time of injection.
At 6 months the basal insulin dose was approximately 18% higher with Toujeo than with Lantus. In the Toujeo group insulin dose increased from 0.38 units/kg/day at baseline to 0.47 units/kg/day at 6 months, and in the Lantus group it increased from 0.37 units/kg/day at baseline to 0.40 units/kg/day at 6 months. However, this was complicated by the additional randomisation to morning and evening use. In the Toujeo group, the basal insulin dose increased with both morning injections (from 0.38 units/kg/day at baseline to 0.49 units/kg/day at month 6) and evening use (from 0.38 units/kg/day at baseline to 0.45 units/kg/day at month 6). However, in the Lantus group, the basal insulin dose increased with morning injections (from 0.38 units/kg/day at baseline to 0.45 units/kg/day at month 6) but not with evening use (0.37 units/kg/day at baseline and 0.36 units/kg/day at month 6). In both groups, the mealtime insulin doses were comparable and were almost unchanged during the study.

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

Safety and tolerability

In EDITION 4, the number of participants with any adverse event or any serious adverse event was similar in the once-daily insulin glargine 300 units/ml (Toujeo) and the once-daily insulin glargine 100 units/ml (Lantus) groups. See table 1 for details. Similar numbers of participants reported injection site reactions (2.2% with Toujeo and 1.5% with Lantus), and similar numbers withdrew because of adverse effects (1.1% with Toujeo and Lantus). One participant in the Toujeo group who had pre-existing cardiovascular disease died of a cardiac event during the 6-month study period.

In EDITION 4, body weight increased with both Toujeo and Lantus, but at month 6 the mean increase was smaller with Toujeo (0.5 kg) than with Lantus (1.0 kg; p=0.037).

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. Overall, serious adverse events were reported by 5.4% of people in both Toujeo and Lantus groups; most commonly hypoglycaemia in people with type 1 diabetes (3.0% with Toujeo, 3.9% 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 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.

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.
Evidence strengths and limitations

There are several limitations with EDITION 4, which the authors discuss. The trial was 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.

The pre-defined hypoglycaemia category was all confirmed (≤70 mg/dl [3.9 mmol/litre]) or severe hypoglycaemia, but the trial was not powered to detect a difference in this between groups because these events affect nearly everyone over 6 months (93.1% with Toujeo and 93.5% with Lantus for anytime of the day; 68.6% with Toujeo and 70.2% with Lantus for nocturnal). Most of the hypoglycaemia events in EDITION 4 occurred during the day. These could have been related to prandial rather than basal insulin, although 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, especially in type 1 diabetes.

The baseline characteristics were largely similar between groups in EDITION 4. However, more people transferred from insulin glargine in the Toujeo group (85.0% compared with 78.5% in the Lantus group). Pre-breakfast self-measured plasma glucose and clinic-measured fasting plasma glucose were also lower in the Toujeo group. Discontinuation of treatment insulin before 6 months was 16% in the Toujeo group and 14% in the Lantus group.

EDITION 4 was 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 limit was 0.19%, which is well below the more desired margin of 0.3%. End points were analysed in the modified intention to treat population using a mixed model for repeated measurements (MMRM) approach. There are no data reported in the published paper or the EPAR for the per-protocol population, which would be usual for a non-inferiority study.

The primary endpoint of EDITION 4, which was conducted in 549 people with type 1 diabetes, was HbA1c at 6 months. An extension study to 12 months has been completed, but not yet published. 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. 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. However, both these trials were conducted in people with type 2 diabetes not type 1 diabetes. In ETDRS, the development or progression of diabetic retinopathy was similar with Lantus or NPH insulin; and in ORIGIN, cardiovascular outcomes were similar with Lantus or standard care (non-insulin therapy).

Context

Alternative treatments

Basal insulin supply for adults with type 1 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

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<th>5×3 ml cartridge</th>
<th>5×3 ml pre-filled pen</th>
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<td>NPH (isophane) insulin 100 units/ml solution</td>
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Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) (ESNM62)
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. In adults with type 1 diabetes, Toujeo is used once-daily with meal-time insulin and requires individual dose adjustments.

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 type 1 diabetes mellitus, it must be combined with short or rapid-acting insulin to cover mealtime insulin requirements.

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). Due to the higher concentration, 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 study of Toujeo in type 1 diabetes, **EDITION 4**, similar numbers of people reported injection site reactions in both groups (2.2% with Toujeo and 1.5% 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 4**. However, based on the mean insulin dose at 6 months, for a 75 kg adult, these are calculated to be 35 units in 0.1 ml for Toujeo and 30 units in 0.3 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. This implies that the reduced volume with Toujeo may not be a particular advantage in people with type 1 diabetes, who generally don't have large basal insulin requirements. It may be more of an advantage for certain people with type 2 diabetes who are insulin resistant and are using very high basal insulin doses.

**EDITION 4** was 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. **EDITION 4** did show that Toujeo had similar efficacy to Lantus in people with type 1 diabetes. However, there was no difference in the risk of hypoglycaemia in this trial. The EPAR states that in people with type 1 diabetes the only advantage is the reduction in injection volume. It states that the more gradual glucose lowering effect of Toujeo compared with Lantus did not translate into important advantages in people with type 1 diabetes, and the higher use of basal insulin may be a disadvantage. In order to obtain a similar effect on HbA1c, 18% higher doses of Toujeo than Lantus were used in people with type 1 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**. Educational material for **healthcare professionals** and **patients** has been produced as an additional
risk minimisation measure. However, no specific advice for people who manage their own insulin dosing by estimating the carbohydrate in each meal seems to be available.

The updated NICE guideline on type 1 diabetes in adults: diagnosis and management recommends twice-daily insulin detemir as the preferred basal insulin therapy. Other basal insulin regimens, including once-daily insulin glargine can also be considered in certain circumstances. When choosing an alternative insulin regimen, the guideline recommends that the person's preferences and acquisition cost should be taken into account, and that people should have access to the insulin injection delivery device they find allows them optimal wellbeing. Toujeo was not considered specifically in the guideline because it was not available when the guideline was produced.

**Estimated usage**

The manufacturer estimates that the uptake of insulin glargine 300 units/ml (Toujeo) for people with type 1 and type 2 diabetes 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). The methodology used to arrive at this estimate is unclear.

**Relevance to NICE guidance programmes**

NICE has issued a guideline on type 1 diabetes: the diagnosis and management of type 1 diabetes in adults.

**References**

Home PD, Bergenstal RM, Bolli GB et al. (2015) New insulin glargine 300 units/ml versus glargine 100 units/ml in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care published online before print, doi: 10.2337/dc15-0249

**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.
Expert advisers

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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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