New Medicine Assessment

Insulin glargine 300 units/mL (Toujeo®)

Treatment of type 1 diabetes mellitus in adults

Recommendation: Amber 0

Insulin glargine 300 units/mL (Toujeo®) is recommended as an option in adults with type 1 diabetes mellitus (T1DM) only in accordance with the recommendations in NICE NG17 and in those who experience an unacceptable frequency and/or severity of nocturnal hypoglycaemia on attempting to achieve better glycaemic control during treatment with first-line long-acting insulin analogues; or as a once daily insulin therapy for patients who require assistance with administering injections.

In T1DM NICE NG17 recommends multiple daily injection basal-bolus insulin as the regimen of choice in all adults with T1DM. Twice-daily insulin detemir is the preferred basal insulin, with once-daily insulin glargine/insulin detemir only being considered if twice-daily basal insulins are not acceptable. Other basal insulin regimens should only be considered if these regimens do not deliver agreed targets (recommended as HbA1c level of 48 mmol/mol (6.5%) or lower). When choosing an alternative insulin regimen person's preferences and acquisition cost should be taken into account.

Insulin glargine 300 units/mL (Toujeo®) was non-inferior to once-daily insulin glargine 100 units/mL (Lantus®) for glycaemic control. Rates of hypoglycaemia did not differ between treatment groups, however, there was a statistically significant difference in change in body weight at 6 months for insulin glargine 300 units/mL (Toujeo®) compared to insulin glargine 100 units/mL (Lantus®)

Summary of supporting evidence:

- One pivotal phase III randomised controlled open-label 4 arm parallel-group study in people with T1DM (EDITION 4) (n=549) was identified. The treatment duration was 6 months, initially, followed by a 6 month extension period (not yet published). Mean baseline HbA1c was 8.1% (65 mmol/mol). Patients were excluded if they had an unstable insulin dose, HbA1c < 7.0% (53 mmol/mol) or > 10% (86 mmol/mol) or had been on a basal insulin plus meal-time insulin regimen for < 1 year.
- Participants were randomised to insulin glargine 300 units/mL (Toujeo®) or insulin glargine 100 units/mL (Lantus®) and titrated weekly to a pre-breakfast self-measured plasma glucose of 80-130 mg/dL (4.4-7.2 mmol/l).
- Once-daily insulin glargine 300 units/mL (Toujeo®) demonstrated non-inferiority to once-daily insulin glargine 100 units/mL (Lantus®) in terms of HbA1c reduction from baseline to month six in patients with T1DM; difference between groups 0.04% (0.4 mmol/mol) [95% CI -0.10 to 0.19% (-1.1 to 2.1 mmol/mol)] – which was below the pre-specified non-inferiority margin of 0.4%. 16.8 % and 15.0% of patients achieved a HbA1c of < 7.0% for Toujeo® and Lantus® respectively.
- Rates of hypoglycaemia did not differ between insulin glargine 300 units/mL (Toujeo®) and insulin glargine 100 units/mL (Lantus®); the number of participants experiencing at least one hypoglycaemic event over 6 months was 93.1% vs. 93.5% respectively [RR 1.00 (95% CI 0.95 to 1.04)].
- Rates of nocturnal hypoglycaemic episodes did not differ between insulin glargine 300 units/mL (Toujeo®) and insulin glargine 100 units/mL (Lantus®) with 68.6% vs. 70.2% respectively experiencing at least one event over 6 months [RR 0.98 (95% CI 0.88 to 1.09)].
- There was a statistically significant difference in change in body weight at 6 months for insulin glargine 300 units/mL (Toujeo®) compared to insulin glargine 100 units/mL (Lantus®) of -0.6 kg [95% CI -1.1 to -0.03) (p= 0.037)].

Safety:

- Insulin glargine 300 units/mL (Toujeo®) is not bioequivalent to insulin glargine 100 units/mL (Lantus®) and dose adjustment would be needed when people are switched from Lantus® (or other basal insulins) to Toujeo® (or vice versa). See MHRA Drug Safety Update April 2015 for risk minimisation recommendations for high strength insulins.
- The European Public Assessment Report for Toujeo® evaluated all people from phase 1, 2 and 3 studies who were randomised and received at least one dose of Toujeo® for safety. Across all studies (n=1546 for

Toujeo® and n=1550 for Lantus®) the number and overall pattern of adverse events was comparable for both groups.
- The most frequent adverse events were; nasopharyngitis (8.2% with Toujeo®, 6.8% with Lantus®) and upper respiratory tract infections (6.5% with Toujeo, 5.8% with Lantus)
- Serious adverse events were reported by 5.4% of people in both Toujeo® and Lantus® groups; most commonly hypoglycaemia in people with T1DM (3.0% for Toujeo® and 3.9% for Lantus®).

Strengths and limitations:

- There are several limitations to EDITION 4, which the authors discuss:
  - The trial was open-label (due to the differences in the pen injectors for the two preparations) which could lead to bias.
  - There was concern over possible confounding by adjustment of the prandial dose.
  - The study was not powered to detect statistical significance for the pre-defined category of hypoglycaemia. Most of the hypoglycaemic events in EDITION 4 occurred during the day which could have been related to the prandial rather than basal insulin, although the prolonged action of Toujeo® may have caused a relative shift of long-acting insulin from night to day.
  - The EPAR states that although the pre-specified non-inferiority margin of 0.4% [4.4 mmol/mol] is considered too wide, the actual upper limit was 0.19% which is well below the more desired 0.3%.
  - Endpoints were analysed in the modified intention to treat population using a mixed model for repeated measurement (MMRM) approach. No data are reported in the EPAR or published paper for the more usual per-protocol population for a non-inferiority study.
  - There are very limited patient oriented outcome data on macrovascular and microvascular outcomes with Toujeo®, or on the long term safety of this particular formulation.
- High strength insulin preparations have been developed for people with large daily insulin requirements to reduce the number and volume of injections. However the following limitations need to be noted:
  - There was no information on injection site pain with Toujeo® compared to Lantus® in the study. In the phase III study similar numbers of patients reported injection site reactions in both groups (2.2% vs. 1.5% for Toujeo® and Lantus® respectively).
  - The pen is limited to delivering 80 units in one injection (60 units for Lantus®) thereby negating the obvious advantage of less injections for those on high doses (if on >80 units).
  - The basal insulin dose in the trials was higher for Toujeo® than for Lantus® treated patients.
  - The EPAR states that the more gradual glucose lowering effect of Toujeo® compared with Lantus® did not translate into important advantages for people with T1DM and the higher use of basal insulin may be a disadvantage.

Cost:

- Insulin glargine 100 units/mL (Lantus®) for a pack of 5 x 3 mL (cartridges or pens) (300 units/pen) = £41.50 (2.8p/unit).
- Insulin glargine 300 units/mL (Toujeo®) for a pack of 3 x 1.5 mL pens (450 units/pen) = £33.13 (2.5p/unit), a saving of 11% for Toujeo® versus Lantus®.
- However, it should be noted that patients in the Toujeo® group required, on average, higher doses of basal insulin compared to those in the insulin glargine 100 units/mL (Lantus®) group; 0.47 units/kg/day vs. 0.40 units/kg/day respectively – approximately 18% higher (no statistical analysis reported).
- Current expenditure of insulin glargine 100 units/mL across Lancashire is £ 2,120,000. Approximately 10% of diabetes cases are T1DM, so we could approximate that £ 210,000 is for this indication. Assuming a saving per unit of 11% and an increase in units of 18% the estimated additional cost pressure if all T1DM patients were switched from Lantus® to Toujeo® would be in the region of £9,900.
- There is now available an insulin glargine 100 units/mL biosimilar (Abasaglar®) 5 pens (300 units/pen) = £35.28 (2.4p/unit).

Prices taken from MIMS online (November 2015).

Please note a full new medicine review has not been carried out for the production of the above recommendation. NICE (Evidence summary: new medicine 62) has performed a full assessment of the evidence & safety of this medicine and this NICE Evidence summary has been used in the preparation of the local policy recommendation.

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