MTRAC
Midlands Therapeutics Review and Advisory Committee

Considerations for Commissioners
Insulin glargine 300 units/mL *(Toujeo®)*

For the treatment of type 1 and type 2 diabetes in adults

Commissioning considerations:

When making a decision about the use of this new formulation of insulin glargine, commissioners may wish to consider the following:

- That people are receiving appropriate treatment with a long-acting insulin analogue according to the current NICE guidance, and that adequate arrangements are in place for regular monitoring and review of patients' diabetes medications. In the National Diabetes audit (2012/13), 80% of people with Type 1 diabetes and 93% of people with Type 2 diabetes had an annual check for the effectiveness of diabetes treatment.
- It may be appropriate to initiate Toujeo treatment in new patients in the first instance, or patients assessed to need a medication change, until clinical experience of the treatment and its delivery device has been gained.
- The committee considered that the place of Toujeo in the diabetes care pathway may be in people previously receiving insulin glargine but experiencing nocturnal hypoglycaemia.
- Draft MHRA guidance suggests that prescribers ensure that patients read and understand the patient information leaflet, receive appropriate training on correct use, are given a patient booklet and insulin passport and should be warned only to use insulins as they have been trained.
- The yearly cost of Toujeo is the same as Lantus (with use of a 12.74% higher dose requirement for Toujeo *vs.* Lantus[†]). The cost for Lantus (assuming a 40-unit daily total dose) is £404 per patient per year, and the cost for Toujeo (assuming a 45 unit daily total dose) is £403.

Strength of the evidence

To gain license approval from the European Medicines agency (EMA) the manufacturer had to demonstrate that Toujeo had a similar safety and efficacy profile to that of the reference product, Lantus.[1] The committee considered that the evidence from four phase 3a randomised controlled trials (RCTs: EDITION study program) adequately demonstrated non-inferiority of Toujeo to Lantus. Adverse effects reported were similar between Toujeo and Lantus.

[†]*Percentage increase in weighted average dose of Toujeo vs. Lantus from all trials in the EDITION program. Data supplied by manufacturer.*

Description of technology

Toujeo (Insulin glargine 300 units/mL) has the same composition as Lantus (insulin glargine 100 U/mL), except with three times the amount of active pharmaceutical ingredient and corresponding zinc content.

Toujeo is indicated for the treatment of diabetes mellitus in adults. It is a basal insulin for once-daily administration at any time of the day, preferably at the same time. The Toujeo dose regimen (dose and timing) should be adjusted according to individual response. In type 1 diabetes mellitus, Toujeo must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements. In patients with type 2 diabetes mellitus, Toujeo can also be given together with other anti-hypoglycaemic medicinal products. The Summary of Product characteristics (SPC)[2] states that "Insulin glargine 100 units/mL and Toujeo are not bioequivalent and are not directly interchangeable. When switching from insulin glargine 100 units/mL to Toujeo, this can be done on a unit-to-unit basis, but a higher Toujeo dose (approximately 10-18%) may be needed to achieve target ranges for plasma glucose levels." The committee noted that doses are dispensed by unit rather than volume, thus reducing the potential for over or under-dosing. See the SPC for full details.

Background

Diabetes mellitus is a common chronic disease, associated with markedly increased morbidity and mortality. It is estimated that in the UK< more than 1 in 16 people in the UK has diagnosed or undiagnosed diabetes, and there are 3.9 million people living with the disease.[3] This number is estimated to rise to 5 million people by 2025.[3] Diabetes is associated with serious long-term microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular complications (coronary heart disease, stroke, and peripheral vascular disease).[4] About 90% of people with diabetes mellitus have type 2 diabetes.[3]

Adults with type 1 diabetes must inject insulin several times daily; a combination of long- and short-acting insulins to replace normal insulin production from the pancreas. NICE guidance on diagnosis and management of type 1 diabetes in adults advises the use of twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. Once daily insulin glargine or insulin detemir could be considered if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated.[5]

Type 2 diabetes is mainly treated with dietary and

lifestyle modification; most patients will eventually need an antidiabetic drug and/or insulin. Treatment currently available includes sulphonylureas, metformin, pioglitazone, acarbose, prandial glucose regulators (repaglinide and nateglinide), DPP-4 inhibitors, GLP-1 analogues (exenatide, liraglutide, dulaglutide, and lixisenatide), SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) and insulin.

Clinical evidence for efficacy and safety

Four phase 3a, open-label RCTs[6-11] of 6 months duration, compared insulin glargine 300 units/mL (Toujeo) with the reference insulin glargine 100 units/mL (Lantus) formulation for the treatment of diabetes.

The EDITION 1[6,7] and EDITION 2 trials[8,9] (n = 807, 811 respectively) evaluated Toujeo *vs.* Lantus in adults with type 2 diabetes, using a combination of basal and mealtime insulin, and who had HbA_{1c} levels of 7.0 to 10.0% (≥ 53 to ≤ 86 mmol/mol). These trials also provided data from six-month extension studies. The EDITION 3 trial (n = 878)[10] evaluated Toujeo *vs.* Lantus in adults with type 2 diabetes, treated with oral antidiabetic drugs for at least 6 months before screening, and who were insulin-naïve. The EDITION 4 trial (n = 549)[11] evaluated adults with type 1 diabetes treated with a basal insulin and a mealtime insulin analogue for at least 3 months.

The primary outcome in the trials was the change in HbA_{1c} from baseline to 6 months. Other outcomes were the percentage of participants with one or more confirmed (self-monitored plasma glucose [SMPG] ≤ 3.9 mmol/L), or severe nocturnal hypoglycaemic events, reported between the start of week 9 and month 6, and the percentage of participants achieving HbA_{1c} ≤ 7.0% (53 mmol/mol). All four trials were designed to show non-inferiority of Toujeo *versus* Lantus based on the change in HbA_{1c} from baseline to endpoint at Month 6 with a non-inferiority margin of 0.4% HbA_{1c}.

Results

Change in HbA_{1c} from baseline to 6 months: this was not significantly different between Lantus and Toujeo in any of the trials. In the EDITION 1 & 2 trials, HbA_{1c} levels decreased by about 0.8% or 9 mmol/mol from a baseline of 8.1% or 65 mmol/mol. In the EDITION 3 trial, HbA_{1c} levels decreased by 1.4% or 15-16 mmol/mol from a baseline of 8.2% or 66 mmol/mol. In the Edition 4 trial, HbA_{1c} levels decreased by about 0.4% or 5 mmol/mol from a baseline of 8.1% or 65 mmol/mol. The mean difference between treatments did not exceed 0.17% or 2 mmol/mol for any of the comparisons of Toujeo and Lantus, and criteria for non-inferiority were met.

Percentage of participants with one or more confirmed or severe nocturnal hypoglycaemic events: A patient-level meta-analysis of data from the Edition 1, 2 and 3 trials,[12] found that the cumulative mean number of nocturnal confirmed or severe hypoglycaemic events was lower with Toujeo than Lantus. Similarly, annualized rates of nocturnal events over the 6-month study period were lower with Toujeo (2.10 *vs.* 3.06, rate ratio 0.69; 95% CI 0.57 to 0.84; p=0.0002), showing a relative difference in rate of 31% in favour of Toujeo. The meta-analysis also reported lower rates of severe hypoglycaemic events and symptomatic hypoglycaemic events occurring at any time for Toujeo *vs.* Lantus.[12]

The percentage of participants achieving HbA_{1c} <7% was not significantly different between treatment groups for this outcome in any of the trials. The percentages of participants achieving the outcome was 15-17% in EDITION 4, 30% and 40% in EDITION 2 and 1, respectively, and 42-43% Edition 3.[10]

Less ***weight gain*** was reported with Toujeo *vs*. Lantus in three trials[8,10,11] and the difference was statistically significant in two trials[8,11].

Adverse events

The most common adverse events reported in the EDITION trials were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups. Injection site reactions were reported in 1-3% of participants in the EDITION 1, 2 and 4 trials and 4-5% of participants in the EDITION 3 trial.[10] The SPC reported hypoglycaemia, lipohypertrophy and injection site reactions as common or very common adverse reactions.[2]

Considerations for cost impact

- From 2013/14 QOF data there were 2,814,004 patients in England with diabetes mellitus recorded in QOF disease registers (average prevalence 6.21%) in adults over 17. In the Midlands and East of England Commissioning region there were 890,000 patients with diabetes mellitus recorded, of which 185,808 are from subscriber CCGs (average prevalence 7.44%).[13]

References

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