East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	**Insulin Glargine high-strength 300 units/ml (Toujeo) in Type 1 Diabetes Mellitus**
Requested by	

SUMMARY

Clinical Effectiveness

The main phase 3 study for insulin glargine 300units/ml (Toujeo) in people with type 1 diabetes was the EDITION 4, a open label randomised controlled trial (n=549) designed to demonstrate non-inferiority with insulin glargine 100units/ml (Lantus) in terms of HbA1c reduction after 6 months of treatment.[1] An extension study to 12 months has not yet been published.

EDITION 4 results[1]:

- Once-daily insulin glargine 300units/ml was non-inferior to once-daily insulin glargine 100units/ml in HbA1c reduction from baseline to month 6 in people with type 1 diabetes.
- Hypoglycaemia (confirmed or severe, nocturnal, or severe) did not differ between insulin glargine 300units/ml and insulin glargine 100units/ml at 6 months in people with type 1 diabetes. (The Forrest Plot from the Edition 4 study shows all confidence intervals crossing 1 for hypoglycaemia over the 6 month period).

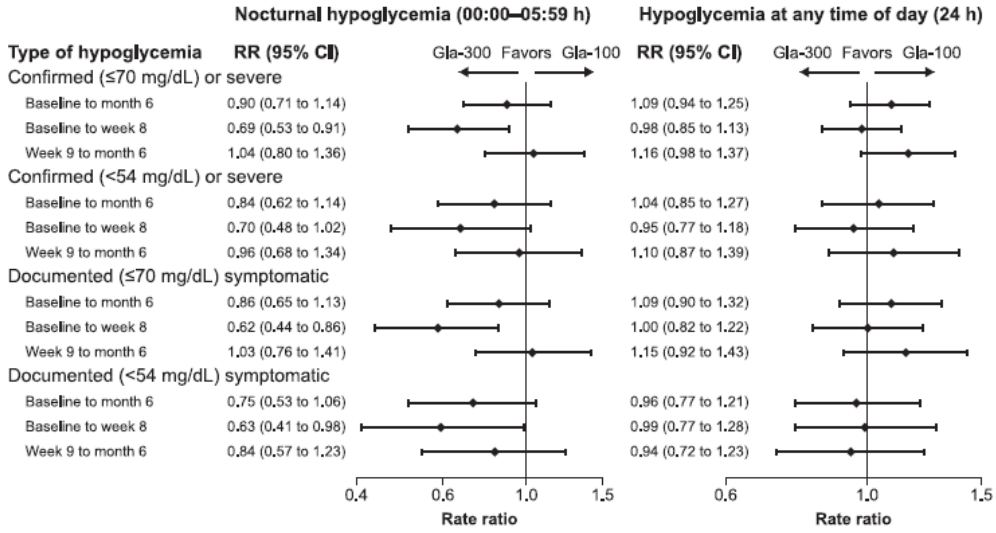

Figure 2—RRs of hypoglycemic events (events/person-year) for the defined nocturnal period and for any time of day (24 h) with Gla-300 vs. Gla-100 during 6 months of treatment (safety population).

A reduced rate of nocturnal (confirmed or severe) hypoglycaemia was reported during the first 8 weeks of treatment with insulin glargine 300units/ml compared to insulin glargine 100units/ml however this reduction was not observed during the remainder of the six months.

- Body weight increased less with insulin glargine 300units/ml than with insulin glargine 100units/ml (mean increase at 6 months 0.5 kg compared with 1.0 kg; p=0.037 Difference = -0.6kg (95% CI -1.1 to -0.03)
- At 6 months the basal insulin dose was approximately 18% higher with insulin glargine 300units/ml than with insulin glargine 100units/ml.

There are very limited patient-oriented outcome data for the effects of insulin glargine 300units/ml on

microvascular and macrovascular outcomes.

High strength insulin products have been developed for people with large daily insulin requirements to reduce the number and volume of injections in order to make them less painful. However there was no information on injection site pain with insulin glargine 300units/ml compared to insulin glargine 100units/ml in the Toujeo study programme. In the EDITION 4 study similar numbers of people reported injection site reactions in both the insulin glargine 300units/ml and insulin glargine 100units/ml groups. In addition the Toujeo Solostar pen device is limited to 80 units per injection so patients requiring higher doses than 80 units will need more than one injection.

Safety

EDITION 4 results[1]:
The safety profile of insulin glargine 300 units/ml (Toujeo) is largely similar to that of insulin glargine 100 units/ml (Lantus).
Similar numbers of participants reported injection site reactions with insulin glargine 300 units/ml (2.2%) and insulin glargine 100 units/ml (1.5%), and similar numbers withdrew because of adverse events (1.1% in both groups).

There is very limited long term safety data for the high strength insulin glargine 300 units/ml.

Patient factors

Toujeo is a high-strength insulin. In clinical trials the dose of Toujeo required was higher than with other insulin glargine preparations. Toujeo 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. Education materials for healthcare professionals and patients have been produced to reduce the risk of medication error resulting from the different strength of the product.
Toujeo is given once daily, preferably at the same time but can be up to 3 hours before or after usual time.
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 though the evidence for this being a benefit for patients is limited.
The Toujeo Solostar pen device is limited to 80 units per injection so patients requiring higher doses than 80 units will need more than one injection.

Cost implications

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. Using the average doses in the EDITION 4 study the cost of Toujeo would be £313 pa and the cost of Lantus £302. A biosimilar insulin glargine 100 units/ml preparation (Abasaglar) is now available at a 15% lower cost than Lantus.

Relevant guidance / reviews

NICE evidence summary (new medicine): Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) published 13 October 2015.[2]
UKMI In Use Safety assessment report for Toujeo and Abasaglar (insulin glargines)[3]
NICE Guideline on type 1 diabetes in adults: diagnosis and management.[4] (Toujeo was not considered specifically as it was not available when the guidelines were produced).
MHRA Drug Safety Update April 2015 High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error.[5]
Scottish Medicines Consortium advice on insulin glargine (Toujeo).[6]

Likely place in therapy relative to current treatments

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. However the majority of diabetes mellitus patients who require high doses of basal insulin are likely to be type 2 diabetes mellitus patients who are insulin resistant.
A reduced rate of nocturnal hypoglycaemia with high strength insulin glargine compared to standard strength product reported during clinical trials in type 1 diabetes during the first 8 weeks was not seen to continue for the remainder of the six months.[1]
There is little published evidence that this higher strength insulin offers additional patient benefits in type 1 diabetes mellitus compared to standard strength insulin glargine preparations. There are alternative formulations of once daily insulin glargine available at a lower cost than Toujeo.

Recommendation to PCN
Options to consider for use of high strength insulin glargine 300units/ml (Toujeo) in type 1 diabetes mellitus: 1. Approve for use in all adult type 1 diabetes mellitus patients 2. Approve for use within NICE guidelines 17 for insulin glargine preparations 3. Approve for use with SMC resistrictions for high strength insulin glargine 4. Do not approve for routine use in type 1 diabetes mellitus patients

Medicine details	
Name and brand name	High Strength insulin glargine 300 units/ml (Toujeo)
Licensed indication, formulation and usual dosage	Licensed indication: Treatment of diabetes mellitus in adults Formulation: 1.5ml of solution for subcutaneous injection in a pre-filled pen Dosage: once daily administration with individual dose adjustments. In type 1 diabetes mellitus it must be combined with a short/rapid-acting insulin to cover mealtime insulin requirements.
Summary of mechanism of action, and relevant pharmacokinetics	Insulin glargine regulates glucose metabolism by lowering blood glucose levels. It stimulates glucose uptake (especially by skeletal muscle and fat), inhibits hepatic glucose production, inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis. Upon injection into subcutaneous tissue the insulin glargine is neutralised leading to the formation of a precipitate from which small amounts of insulin glargine are continuously released. Toujeo has a flatter and more prolonged (upto 36 hours) profile of insulin concentration and glucose lowering activity compared to Lantus at the same doses.
Important drug interactions	
Monitoring requirements	Metabolic monitoring requirements are similar to that required for other insulin preparations.
Prescribing considerations	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. Education materials for healthcare professionals, patients and carers have been produced to reduce this risk. The manufacturer recommends that the product is prescribed by brand to minimise confusion. Patients should be issued with an insulin passport. Toujeo is not bioequivalent to insulin glargine 100 units/ml and a dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa. Close metabolic monitoring is recommended during the switch and in the initial weeks after. Needles are not included with the product and need to be prescribed separately along with a suitable sharps container. Blood glucose testing strips will also need to be prescribed and a meter supplied. A short or rapid acting insulin will need to be added to cover mealtime requirements in type 1 diabetes.
Other considerations	

Potential patient group (if appropriate to include)	
Brief description of disease	Type 1 diabetes mellitus High-strength insulin products have been developed for people with large daily insulin requirements to reduce the number and volume of injections
Potential patient numbers per 100,000	The manufacturer estimates that the uptake of insulin glargine 300 units/ml (Toujeo) in both type1 and type 2 diabetes in England will be as follows[2]: 2015 734 people 2016 9,994 people 2017 27,900 people 2018 65,386 people 2019 80,948 people 2020 90,581 people The methodology used to arrive at the estimate is unclear.
Outcomes required	

Summary of current treatment pathway

NICE guideline on type 1 diabetes in adults: diagnosis and management[4] 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 and once daily insulin glargine or insulin detemir can be considered if twice daily basal insulin injections are not acceptable. Other insulin regimes can be considered if the patient is already using these successfully or if the NICE recommended regimes have not delivered the agreed targets.

Insulin glargine 100units/ml (Lantus) has not been considered by the **PCN** for type 1 diabetes.
Lantus was considered by the PCN in June 2011 for type 2 diabetes and given a GREEN traffic light status:
Surrey Area Prescribing Committee recommends the following in relation to insulin treatment for patients with type 2 diabetes:

- Insulin initiation should be tailored to meet the needs of the patient.
- If a patient requires basal insulin the neutral protamine hagedorn (NPH) insulin should be used with consideration to change to an analogue should the patient experience problems with hypoglycaemia and/or weight gain.
- If patients require prandial cover then the rapid-acting analogues should be used.
- If the patient requires mixed insulin then mixed analogue insulin should be used

The biosimilar insulin glargine 100 units/ml preparation (Abasaglar) will be considered by the PCN in the near future.

Evidence review

NICE Evidence summary (new medicine): Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) October 2015.
https://www.nice.org.uk/advice/esnm62

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs	**Surrey and Sussex Healthcare NHS Trust** DTC decision 20th October 2015: Committee supported the introduction of Toujeo but agreed to await consideration at the next PCN as the trust doesn't want to initiate patients without GP support. **Royal Surrey County Hospital NHS Foundation** Trust DTC decision 6th 2015: Approved for inclusion on the formulary for : · People with type 1 diabetes who have experienced nocturnal hypoglycaemia on a basal bolus insulin regime · People with type 2 diabetes who have experienced nocturnal hypoglycaemia on a basal or basal bolus insulin regime It will be a RED drug supplied by the hospital until the PCN has taken a decision on the traffic light status.
Recommendations from national / regional decision making groups	The **Scottish Medicines Consortium** has accepted Toujeo for restricted use within NHS Scotland in adults with Type 1 diabetes mellitus.[6] It recommeded its use should be targeted on patients with Type I diabetes who are at risk of or experience unacceptable frequency and/or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with established insulins. It also recommeded that it is acceptable as a once daily insulin therapy for patients who require carer administration of their insulin. In the US the **FDA** did not acknowledge that the drug led to fewer cases of overnight hypoglycaemia in its approval ruling. Sanofi is therefore unable to market the drug with this claim in the country, making it harder to differentiate it from Lantus.[7]
Stakeholder views	Local endocrinologists and other stakeholders have been contacted for their views on Toujeo in type 1 Diabetes Mellitus and the stakeholder views will be below in 'comments received'
CCG priorities	

Health economic considerations

Cost per year per patient

The cost of Toujeo is £33.13 for 3×1.5 ml pre-filled pens

The average Toujeo daily dose requirement in the EDITION 4 trial was 35 units for a 75kg adult. This is equivalent to approx. 9.46 boxes of Toujeo Solostar prefilled pens per year costing **£313**.

Alternative treatments cost per patient per year

The average Lantus daily dose requirement in the EDITION 4 trial was 30 units for a 75kg adult. This is equivalent to approx. 7.3 boxes of Toujeo Solostar prefilled pens per year costing **£302**.

Insulin prices:

NPH Isophane insulin 100 units/ml (Humulin I)	5x3ml pen refills	£19.08
Insulin detremir 100 units/ml (Levemir)	5x3ml pen refills	£42.00
Insulin Glargine 100 units/ml (Lantus)	5x3ml prefilled pens or cartridges	£41.50
Insulin Glargine 100 units/ml (Abasaglar) (biosimilar)	5x3ml prefilled pens or cartridges	£35.28
Insulin Glargine 300 units/ml (Toujeo)	3x1.5ml prefilled pen	£33.13

(All prices excluding VAT; MIMS, September 2015).

Other financial considerations (if relevant)

Health economic data (if available)

References

1. Home PD, Bergenstal RM, Bolli GB et al. New Insulin Glargine 300 units/ml versus glargine 100 units/ml in people with type 1 diabetes: a randomised phase 3a open label clinical trial (EDITION 4). *Diabetes Care 2015; 38: 2217-2225*
   Published online before print June 17, 2015, doi: 10.2337/dc15-0249
2. NICE Evidence summary (new medicine): Type 1 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) October 2015
   Available from
   https://www.nice.org.uk/advice/esnm62
3. UKMI In Use Safety assessment report for Toujeo and Abasaglar (insulin glargines) October 2015
   Available from
   http://www.ukmi.nhs.uk/filestore/ukmiaps/InsulinglarginesOct-2015_1.pdf
4. NICE Guideline on type 1 diabetes in adults: diagnosis and management. August 2015.
   Available from
   https://www.nice.org.uk/guidance/ng17
5. MHRA High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error**.** *Drug Safety Update* 8 (9) 3-5 April 2015
6. Scottish Medicines Consortium. Advice on insulin glargine (Toujeo). September 2015.
   Available from
   https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1078_15_insulin_glargine_Toujeo/insulin_glargine_Toujeo_ABB
7. UKMI New Drugs online. Insulin glargine U300.
   Available frpm
   http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=6085

Date: 16th December 2015

Prepared by: Deborah Bunn, Primary Care Pharmacist (East Surrey), Surrey Downs CCG (Hosted Service).
Declaration of interest: No current potential conflicts of interest

Reviewed by: Helen Marlow, Lead Primary Care Pharmacist, Surrey Downs CCG Declaration of interest: See below