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Answers to commonly asked questions about biosimilar versions of insulin glargine

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The first biosimilar version of insulin glargine (Abasaglar®) was approved for use in Europe in September 2014 and was launched in the UK in September 2015. It is licensed identically to the originator product (Lantus®), for use in the treatment of type 1 and type 2 diabetes mellitus in adults, adolescents and children aged 2 years and above. Two further insulin glargine biosimilars are currently in the pipeline, with UK launches anticipated over the next two years. This briefing sheet is intended to support prescribers by providing answers to commonly asked questions about the introduction of these medicines.

What is a biosimilar medicine?

A biosimilar medicine is a biological medicine that is similar to a medicine that has already been authorised to be marketed in the EU (the biological reference medicine) with respect to quality, safety and efficacy. Information on biosimilar medicines and the background to their licensing and clinical use are discussed in an open access article from the Drug & Therapeutics Bulletin entitled; What are biosimilars and are they important? (1). A guide on biosimilars is also available from NHS England; this is intended to provide an update for stakeholders about their developing role in the NHS and can be used locally to inform finance and procurement discussions (2).

What brands of insulin glargine will be available for use?

One insulin glargine biosimilar (Abasaglar®; Eli Lilly) is currently licensed in the UK and was launched on 9th September 2015 (3, 4). The primary amino acid sequence of the biosimilar is the same as that of the active ingredient in the reference medicine (Lantus®), and the therapeutic indications, pharmaceutical form (solution for injection) and strength (100 units per mL) are also identical (5). Although there are some differences in excipients used in the formulation of the biosimilar (zinc oxide replaces zinc chloride; 100% glycerol versus 85% in Lantus®), the final quantitative formulation is the same as that of Lantus® (5).

Sanofi has recently launched a new, more concentrated formulation of insulin glargine (Toujeo®; 300 units per mL). This has a flatter and more prolonged pharmacokinetic/dynamic profile than Lantus® and offers the benefit of a smaller volume of subcutaneous injection (6). It has been launched in the UK with a claimed advantage of a lower incidence of hypoglycaemia than Lantus®; Sanofi is however unable to market the drug with this claim in the US as the FDA did not acknowledge that the drug led to fewer cases of overnight hypoglycaemia in its approval ruling (6). Toujeo® is not a biosimilar of, or bioequivalent to, Lantus® (7). NICE has published an 'evidence summary new medicines' review on Toujeo® in type 1 diabetes which discusses the evidence on its safety and efficacy, including the observed rates of hypoglycaemia (8). An evidence summary on its use in type 2 diabetes is currently in development but will not be available until the updated NICE guideline on type 2 diabetes has been published.

How should insulin glargine be prescribed?

The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that it is good practice to prescribe biological products by brand name to ensure that substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist (9). The use of brand names in all stages of the medicines supply chain for insulin glargine will be essential to allow differentiation between the various forms, which is vital for post-launch pharmacovigilance and to ensure patient safety (avoidance of inadvertent switching). Pharmacists should challenge any prescriptions for insulin by its generic rather than trade name, to ensure that the product dispensed is the correct one intended for the patient (10).

Are there any differences in administration devices for the available brands of insulin glargine?

Abasaglar® is available in the existing Lilly devices – the prefilled Kwikpen® and 3mL cartridges for use in the reusable Savvio® pen (5, 11-12). This is similar to Lantus® – which is also available in 3mL cartridges (for use with compatible pen injectors) and a prefilled pen (SoloStar) (13, 14).

What objections are being raised about using biosimilar versions of insulin glargine?

No specific concerns related to the introduction of insulin glargine biosimilars were identified from a search of the literature.

Previous concerns voiced by clinicians about biosimilars in general relate to their pharmaceutical quality, safety, and their interchangeability with the reference product. They also include doubts about clinical efficacy and safety in extrapolated indications for which no formal clinical studies have been performed with the biosimilar (15). The latter is not as relevant to insulin glargine as there is a clinical trial in both type 1 and type 2 diabetes.

What evidence is required for the approval of biosimilars in the EU?

The regulatory requirements for the approval of a biosimilar are considerably greater than those for a generic drug. For the latter, it is usually sufficient to demonstrate pharmaceutical equivalence (identical amounts of the same active ingredient in the same dose form) and bioequivalence to the reference medicine. However for a biosimilar, a much more comprehensive analysis is required, due to the complexity of these products and their manufacturing processes (16).

A legal pathway for the development of biosimilars (the 'biosimilar pathway') was established in the EU in 2005 and several biosimilars (e.g. somatropins; filgrastims; epoetins) have been licensed since this time (15). The guiding principle of the development of biosimilars is not to establish patient benefit per se (which has already been shown for the reference product), but to demonstrate high similarity to the reference product so that the experience gained with its use can be extrapolated to the biosimilar version (1).

The biosimilar development pathway involves an extensive comparability exercise, which is a head-to-head comparison of the biosimilar with the reference product in order to ensure a close resemblance in terms of physical chemistry, biological characteristics, safety and efficacy (1, 15). It is not expected that the biosimilar will be identical to the reference drug; the purpose of the comparability exercise is to show that the degree of variability is not significant (16). The development pathway follows a stepwise approach, with demonstration of: (17, 18)

- Quality comparability (with regard to the molecular structure and functionality)
- Non-clinical comparability (comparative non-clinical studies)
- Clinical comparability (comparative clinical studies)

The foundation of biosimilar development is the extensive characterisation and comparison of the physiochemical properties and biological activity of the biosimilar and the originator, and the subsequent requirement for non-clinical and clinical data will depend on the observed similarity in these aspects (15). The extent of the non-clinical and clinical studies required to confirm biosimilarity will also depend on the nature and the complexity of the reference product (19). The purpose of clinical data is to provide complementary information; for example the clinical relevance of any observed differences, and data on immunogenicity (15).

What evidence exists to support the use of a biosimilar version of insulin glargine?

A comprehensive comparability exercise was performed for Abasaglar® with the reference product (Lantus®). The initial stage consisted of numerous physiochemical tests and studies comparing biological activity, and the biosimilar was deemed to be comparable to the reference product from a quality perspective (5).

The non-clinical exercise consisted of studies evaluating their similarity in terms of pharmacology and toxicology. There were some concerns raised with respect to the ability of a specific assay used (IR-A phosphorylation assay) to detect subtle differences in binding affinity and potency; reassurance was however provided by the results of further studies conducted by the manufacturer (5).

As well as the overarching biosimilars guideline, the EMA has produced a number of class-specific guidelines, including one on the development of biosimilar insulins (20). This states that pharmacokinetic/ pharmacodynamic insulin clamp studies represent the mainstay of the proof of similar efficacy of the biosimilar and the reference product. The clinical comparability exercise for Abasaglar® included five such studies; two were pivotal, of which one compared it to EU-approved Lantus®. Together these studies, which tested several dose levels and were conducted in both healthy volunteers and individuals with type 1 diabetes, established pharmacokinetic and pharmacodynamic equivalence of Abasaglar® and Lantus®.

The EMA guideline makes it clear that there is no anticipated need for specific efficacy studies, as the endpoints used (usually HbA1c) are not considered sensitive enough for the purpose of showing biosimilarity of two insulins. The data from such studies are therefore considered as supportive evidence of clinical biosimilarity. Two clinical efficacy studies were conducted for Abasaglar®; both had a 24-week treatment period and used treat-to-target approaches to achieve protocol-specified glycaemic goals. The key results from these were as follows (please see table 1 in the Appendix 1 for further details) (5, 21-22):

- ELEMENT 1 (Phase III RCT in patients with type 1 diabetes; n=535): Abasaglar® was non-inferior to Lantus® (both used in combination with pre-meal insulin lispro) in terms of change in HbA1c from baseline to week 24 (-0.35% v -0.46%, respectively; 95% CI of the difference -0.002% to +0.219%).

- ELEMENT 2 (Phase III RCT in patients with type 2 diabetes; n=756): Abasaglar® was non-inferior to Lantus® (both used in combination with oral anti-hyperglycaemics) in terms of change in HbA1c from baseline to week 24 (-1.29% v -1.34%, respectively; 95% CI of the difference -0.070% to +0.175%).

No major safety findings or signals were identified in the clinical programme (5).

An analysis of results for the subgroup of patients who reported use of Lantus® prior to inclusion in either of the ELEMENT studies reported no statistically significant treatment differences for the primary outcomes (23).
For further details of the evidence, please see the NICE 'Evidence summary new medicine' for insulin glargine biosimilar (Abasaglar), which is due for publication in October 2015 (24).

If the clinical studies were conducted in adults, what evidence is there to support use of the biosimilar in children?

Extrapolation is the regulatory and scientific process of granting a clinical indication to a medicine without its own clinical efficacy and safety data to support that indication (16). This is an already established scientific and regulatory principle that has been exercised for many years; it has however recently become the focus of heightened interest following the introduction of biosimilars.

If biosimilarity has been demonstrated in one indication, the EMA considers that extrapolation of efficacy and safety data to all other indications of the reference product may be acceptable with appropriate scientific justifications (18). Although concerns have been expressed about this, the Working Party on Similar Biologic Medicinal Products of the EMA stress that extrapolation will only be approved on the basis of sound scientific justification, and only when the following requirements have been fulfilled (15):

- Similarity with the reference product must be convincingly demonstrated based on the totality of evidence from the comparability exercise
- If the mechanism of action involved in the extrapolated indication(s) is different or unknown, additional convincing data must be available for further reassurance that the biosimilar and the reference product will behave alike in these indications
- The safety profile of the biosimilar must have been properly characterised and unacceptable immunogenicity excluded

The principles of extrapolation have been applied to the approval of all biosimilars currently licensed in the UK (e.g. growth hormone; G-CSF; infliximab), with no significant incidents reported to date.

EMA guidance on the development of insulin biosimilars states that if biosimilarity has been demonstrated with subcutaneous use, with no identified safety issues, then extrapolation to intravenous use (if applicable) and to other indications and patient populations licensed for the reference product is permitted (20).

Will there be any independent guidance available to help inform clinical practice?

NICE has recently clarified its position with regards to the evaluation of biosimilars. Biosimilars notified to the NICE topic selection process for referral to the Technology Appraisal programme will usually be considered in the context of a Multiple Technology Appraisal in parallel with their reference products in the indication under consideration. In other circumstances, where it is considered a review of the evidence for a biosimilar is necessary, NICE will consider producing an ‘Evidence summary new medicine’. Evidence summaries do not make recommendations hence the decision regarding the choice of biosimilar or originator biologic for an individual patient rests with the responsible clinician in consultation with the patient (25). An ‘Evidence summary new medicine’ on the insulin glargine biosimilar (Abasaglar) is due for publication in October 2015 (24).

Diabetes UK issued a position statement on biosimilar insulins in October 2013, in anticipation of their arrival to the UK market (10). This emphasises that decisions regarding the use of biosimilar insulins should be made on a case by case basis, with the informed involvement of the person with diabetes. It is suggested that the biosimilar may be considered as an option for individuals starting insulin treatment or switching to an analogue for optimal control. It does however recommend against switching patients to a biosimilar if they are already established on an insulin and well controlled. If people with diabetes choose to switch to a biosimilar insulin, they should be encouraged and supported to monitor their blood glucose more closely to ensure that good control is achieved (10).

To date, the European Association for the Study of Diabetes and the American Diabetes Association have not released position statements on biosimilar insulins. The Scottish Medicines Consortium (SMC) will not review Abasaglar® following their recent update to the SMC Policy for Biosimilar Medicines. It is however expected to undergo review by the All Wales Medicines Strategy group (AWMSG) in 2015 (11).

The MHRA has issued the following advice for healthcare professionals who are starting patients on a high strength, fixed combination or biosimilar insulin product, to minimise the risk of medication errors (7):

- 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 to because using it any other way may result in a dangerous overdose or underdose
- Monitor glucose levels closely after starting a new treatment and in the following weeks. You may need to adjust doses and timing of concurrent rapid acting or short acting insulin products and other antidiabetic treatments.

What is the current national guidance regarding choice of insulin in patients with diabetes?

Type 1 diabetes

NICE issued updated guidance on the management of type 1 diabetes in adults in August 2015 (26). This recommends twice-daily insulin detemir as the first-line basal insulin therapy; the following alternatives may be considered:

- an existing insulin regimen being used by the person that is achieving their agreed targets
- once-daily insulin glargine or insulin detemir if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated.

Other basal insulin regimens for adults with type 1 diabetes should only be considered if the above recommendations do not deliver agreed targets. The person's preferences and the acquisition cost should be taken into account when choosing an alternative insulin.

Type 2 diabetes

An updated guideline on type 2 diabetes is currently in progress (27). The draft recommendations regarding insulin recommend NPH insulin or twice-daily pre-mixed (biphasic) human insulin. Insulin detemir or insulin glargine can be considered as an alternative to NPH insulin if:

- the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily, **or**
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, **or**
- the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.

Switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes can also be considered in those:

- who do not reach their target HbA1c because of significant hypoglycaemia, **or**
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, **or**

- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made, **or**
- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections.

Type 1 and type 2 diabetes in children

This guideline (August 2015) recommends that children and young people with type 1 diabetes be offered multiple daily injection basal-bolus insulin regimens from diagnosis (or continuous subcutaneous insulin infusion therapy if this is not appropriate). No specific basal insulin is recommended over another (28).

Is there any guidance on switching between Lantus® and the biosimilar?

There is no specific guidance available on substitution of the reference product (Lantus®) with the biosimilar (Abasaglar®). This will however require blood glucose monitoring and may potentially require dosage adjustment.

The two Phase III ELEMENT studies included a subgroup of patients who reported pre-study treatment with Lantus®, so following randomisation they either continued on Lantus® or switched to Abasaglar® (unit-to-unit dose conversion). The insulin dose was titrated as necessary to reach defined glycaemic targets. No difference in dose changes after titration to tighten glucose blood control was reported between the two treatment arms in either study (5).

Are there any potential advantages to using a biosimilar version of insulin glargine?

As biosimilars will likely be available at lower costs than the originator, they have the potential to reduce treatment costs, expand market competition and increase patient accessibility. The cost savings of developing biosimilars compared with their originators is not likely to be as large as those that are achieved by generic drugs compared with their originator products. Nevertheless, the chronic nature of their use in many people can lead to significant absolute cost savings. This will of course be contingent upon their acceptance in the marketplace (16).

Abasaglar® is available at a cost of £35.28 for 5x3mL (for both the cartridges and the prefilled pens). This compares to a cost of £41.50 for the equivalent pack of Lantus® (11, 29). As an example, the difference between the two in annual cost for one patient at a dose of 40 units daily would be around £60.

In 2014, the total spend on insulin glargine (Lantus®) in primary care in England was £78,826,400 (30). If it is assumed that 50% switch to the biosimilar, then this will lead to a saving of approximately £5.9 million, or £11,000 per 100,000 population.

Are there any risks associated with the availability of multiple insulin glargine products?

UKMi has produced an In-Use Product Safety Assessment which summarises the safety considerations associated with the introduction of Abasaglar® and Toujeo® (31).

What safeguards will be in place to ensure that post-marketing safety is being monitored?

Every biosimilar medicine authorised in the EU will have a risk management plan (RMP) in place and information on this is included in the European Public Assessment Report. Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product (15).

The Abasaglar® RMP summarises the important identified (low blood sugar; allergic reactions; injection site reactions; medication error) and potential risks (malignancies; antibody development). This also notes that Abasaglar® has not been studied in pregnant or breastfeeding women, and that insulin glargine in general has not been studied in children less than 2 years of age (32).

Based on consideration of the data submitted, the EMA considered that routine pharmacovigilance and risk minimisation measures (education through the summary of product characteristics and package leaflet) are sufficient to identify, characterise and minimise the risks of the insulin glargine biosimilar (5).

What other biosimilar medicines are expected over the next few years?

Biosimilar versions of the following medicines are currently in development and are expected to be available in the UK over the next couple of years: trastuzumab (Herceptin®); etanercept (Enbrel®); rituximab (MabThera®); and pegfilgrastim (Neulasta®) (33).

What information is available for patients?

A Q&A on biosimilar medicines is available from the EMA (34). In its position statement, Diabetes UK states that it will raise awareness of biosimilar insulins to its lay and professional membership (10); no material is as yet available on its website.

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APPENDIX

Table 1: Main results of the two supportive clinical studies comparing insulin glargine biosimilar (LY2963016; Abasria) to Lantus®

Population and treatment	Primary endpoint(s)	Key secondary endpoints*	Adverse effects
Randomised, open-label Phase III efficacy study (ELEMENT 1)			
535 adults (FAS) with type 1 DM meeting the following criteria: • HbA1c ≤11% • BMI ≤35kg/m^2 • Treated with basal-bolus regimen for ≥1 yr (and on once daily NPH, Lantus® or detemir for ≥3 months) Randomised to once-daily LY2963016 or Lantus® (same dose as prestudy basal insulin; adjustments to meet glycaemic targets) plus premeal insulin lispro for 24 weeks plus 28-week extension (92% completed 52 wks)	**Change in HbA1c from baseline to week 24**: • -0.35% ± 0.05% for LY2963016 • -0.46% ± 0.05% for Lantus® • Difference (LSM) of 0.108%; 95% CI -0.002 to 0.219) The respective results at 52 weeks were -0.26% ± 0.06% -0.28 ± 0.06% for (LSM difference of 0.020; 95% CI -0.099 to 0.140) Non-inferiority determined as the upper limit of the 95% CI on the difference at 24 wks was below the specified margins of 0.4% and 0.3%.	LSM BG values at bedtime and 3 am were lower in the LY2963016 arm at 24 weeks (however small and no difference in nocturnal HG). Comparable findings for other efficacy measures (achievement of target HbA1c; fasting blood glucose, insulin dose, weight changes) at 24 weeks No difference in proportion of patients with detectable anti-insulin antibodies up to 52 wks+	Incidence/severity of AEs similar between groups, including incidence of HG (overall, nocturnal or severe), allergic reactions, and injection site AEs
Randomised, double-blind Phase III efficacy study (ELEMENT 2)			
756 adults (FAS) with type 2 DM meeting the following criteria: • taking ≥2 OAMs (± Lantus®) at stable doses for ≥12 wk • BMI ≤45kg/m^2 • HbA1c ≥7.0% and ≤11.0% (if insulin naïve) or ≤11.0% (if previously on Lantus®) Randomised to once-daily LY2963016 or Lantus® (equivalent dose if on pre-study; 10IU starting dose if insulin-naïve). Patient-driven dosing algorithm used to maintain FPG ≤5.6 mmol/L	**Change in HbA1c from baseline to week 24**: • -1.29% ± 0.06% for LY2963016 • -1.34% ± 0.06% for Lantus® • Difference (LSM) of 0.052%; 95% CI -0.070 to 0.175) Non-inferiority determined as the upper limit of the 95% CI on the difference at 24 wks was below the specified margins of 0.4% and 0.3%.	LSM BG values at the morning 2-hour post-prandial and the midday pre-meal time points were lower in the LY2963016 group at study end (week 24); no statistically significant differences were seen at any other time. Findings for other measures (achievement of target HbA1c; FPG, insulin dose, weight gain) were comparable. No difference in proportion of patients with detectable anti-insulin antibodies+	Incidence/severity of AEs similar between groups, including incidence of HG (overall, nocturnal or severe), allergic reactions, and injection site AEs Higher number of events in the vascular SOC with the biosimilar (5.6% v 2.4%) - thought due to imbalance in pre-existing hypertension

DM: diabetes mellitus; HbA1c: glycosylated haemoglobin; PRN: when required; LSM: least-squares mean; AEs: adverse effects; OAHG: oral antihyperglycaemics; IGlar: insulin glargine; FPG: fasting plasma glucose; HG: hypoglycaemia; FAS: full analysis set (all patients randomised who took at least one dose of study medication); BG: blood glucose

*The observed differences in some secondary endpoints were not deemed clinically relevant when the results of the studies were taken together.

+The proportion of patients with detectable antibodies was comparable throughout both studies, with the exception of the subgroup of patients previously treated with Lantus® in ELEMENT2 (19.2% with the biosimilar v 7.9% with Lantus®). This is likely a chance finding as there was already a difference at baseline, no difference in antibody levels were detected and the finding was not corroborated by data from EMELENT1 (a more sensitive population).