PrescQIPP Community Interest Company

Biosimilar - Insulin glargine

Across the globe diabetes mellitus is recognised as one of the leading causes of death and disability.

It is estimated that 371 million adults have diabetes worldwide. This number is predicted to increase to 552 million by 2030.[1]

Diabetes mellitus is a chronic disease that occurs for one of two reasons:

- The pancreas does not produce enough insulin (type 1 diabetes mellitus - T1DM).
- The body cannot effectively utilise the insulin it produces (type 2 diabetes mellitus -T2DM).

In either scenario hyperglycaemia will ensue.

With both forms of diabetes, close glycaemic control is recommended as this has been shown to reduce the risks of long term complications due to high circulating blood glucose levels. The role of insulin in achieving the required control is well recognised.[2]

Long acting insulin analogues, such as insulin glargine, provide smooth, peakless basal insulin profiles, resulting in a glycaemic profile similar to normal physiology, potentially enabling people to achieve normal blood glucose levels.

Long acting insulin analogues, such as insulin glargine, may provide benefits such as less hypoglycaemia over intermediate and long acting insulin, e.g. isophane insulin (Neutral Protamine Hagedorn (NPH)).[3-7] These benefits are more pronounced in T1DM and include reduced frequency of nocturnal hypoglycaemia, better fasting blood glucose control and improved quality of life. The benefits in T2DM are less distinct and insulin glargine should be used only in selected patients as per National Institute of Clinical Excellence (NICE) guidance.[8]

Insulin glargine was first authorised in the EU on 9 June 2000 under the name of Lantus. It is currently approved for the treatment of diabetes mellitus in adults, adolescents and children aged two years and above.[9] The therapeutic indications and posology for Abasaglar (biosimilar insulin glargine) are identical to those for Lantus.[10]

Recommendations

Initiation of insulin

Type 1 diabetes

- Insulin glargine (Lantus) is recommended as an option for the treatment of T1DM.
- The biosimilar product, Abasaglar®, is an alternative to Lantus.

Type 2 diabetes

- Insulin (NPH) isophane is the treatment of choice for the treatment of T2DM.
- For patients who require an insulin analogue the biosimilar product, Abasaglar®, is an alternative to Lantus or other insulin analogues.

Switching insulin

Type 1 and type 2 diabetes

- Patients with either type 1 or type 2 diabetes should be under regular review to ensure appropriate management of their diabetes and associated complications.
- For patients being treated with insulin glargine (Lantus) these reviews provide an ideal opportunity to discuss the possibility of switching to the alternative biosimilar product.
- Ideally this would involve a discussion around the potential benefits as well as any possible risks.
- The patient should also be made aware that any switch is only to be undertaken with their consent and they would be free to continue with the current insulin if that was their preference.
- Patients must be able to use the insulin pens currently available from Eli Lilly i.e. the KwikPen and HumaPen Savvio.
- Specific training on these devices is essential, the Boehringer-Lilly Alliance are not actively promoting or supporting the switching of patients currently receiving Lantus to Abasaglar®.

Prescribing of insulin glargine

- As with all biosimilar products prescribing by brand name is strongly recommended.
- In order to prevent any inadvertent switching it is also recommended that prescribing of the originator insulin glargine, Lantus, is also by brand name only.

Biological medicinal products are fundamentally different from chemically derived medicines in terms of their production, complexity of chemical structure, purity and immunogenicity.[11]

Biological medicines are produced in or derived from living systems, and are made up of proteins, sugars or nucleic acids.[12] A biosimilar medicine is a medicine that is developed to be similar to an existing biological medicine in terms of efficacy and safety.[13]

Biosimilar medicines differ from generic drugs which have simpler chemical structures and are considered to be identical to their reference medicines.[14] The characteristics of biologic drugs cannot be reproduced exactly due to the complexity of the manufacturing process. Changes in the production site and production process (even minor) can affect the complex three-dimensional structure of a biosimilar medicine and other characteristics such as glycosylation.[15]

These variations in characteristics may affect the biological activity of the biosimilar medicine. The European Medicines Agency (EMA) therefore requires evidence (via pre-clinical studies and phase 1 and 3 clinical studies) that a biosimilar medicine is similar to the reference medicinal product in terms of quality, efficacy and safety. Biosimilar medicines are usually approved via an abbreviated licensing process with a limited clinical database, hence significant post-approval commitments (e.g. pharmacovigilance) are required to further characterise immunogenic potential and monitor adverse drug reactions. In order to support pharmacovigilance monitoring, biosimilar medicines are required to be prescribed by brand name.[16]

Abasaglar® was submitted as a biosimilar medicine, with Lantus (insulin glargine) as the chosen reference medicinal product. Lantus has been marketed in the European Union for over ten years and Lantus 100 unit/ml solution for injection was first authorised in the EU on 9 June 2000.[17]

The primary amino acid sequence of Abasaglar® is the same as that of the active ingredient in Lantus. Abasaglar® has the same pharmaceutical form and strength as Lantus. Abasaglar® differs from the reference medicinal product with respect to excipients used in the formulation: In Abasaglar® zinc oxide replaces zinc chloride and 100% glycerol is used compared with 85% in the reference medicinal product.[18]

However, the final quantitative formulation is the same as that of the reference medicinal product.

Abasaglar® is a long acting insulin analogue administered as a subcutaneous injection for the treatment of diabetes mellitus in adults, adolescents, and children aged two years and above. It is available in two presentations: a 3 mL cartridge, for delivery by a reusable pen injector (HumaPen Savvio), and also the same 3 mL cartridge sealed in a prefilled pen injector (KwikPen).[10]

National guidance

Diabetes mellitus

NICE Guideline 17 on the diagnosis and management of type 1 diabetes recommends the following in relation to long acting insulin:[19]

- Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes.
- Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:
  - 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.
- Consider other basal insulin regimens for adults with type 1 diabetes only if the regimens recommendations above do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost.

The NICE clinical guideline on type 2 diabetes[8] states:

Initiate insulin therapy from a choice of a number of insulin types and regimens.

- Begin with human NPH insulin injected at bed-time or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:
  - The person needs assistance from a carer or healthcare professional to inject insulin, and use of a long acting insulin analogue (insulin detemir, 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, or
  - The person cannot use the device to inject NPH insulin.

There has been a recent push nationwide to encourage the prescribing of NPH insulin to follow these recommendations.[20] This has been in response to the widespread, and often inappropriate, use of insulin glargine as the first choice insulin in T2DM.

Biosimilars

NICE position on biosimilars[21]

Although biosimilars are already used to some extent in the NHS, and NICE has previously included biosimilars in its technology appraisal on the human growth hormone (somatropin), it is likely that their availability and use will become more widespread over the next few years.

Biosimilars have the potential to offer the NHS considerable cost savings, especially as they are often used to treat long term conditions.

Therefore NICE's position and process for developing guidance and advice for these medicines has been reviewed. The recommendations now include the following:

1. NICE will consider biosimilar medicines notified to it by the National Institute for Health Research Horizon Scanning Centre.
2. These products will usually be considered in the context of a Multiple Technology Appraisal in

parallel with their reference products in the indication under consideration.

3. In other circumstances, where it is considered a review of the evidence for similar biological medicinal product is necessary, NICE will consider producing an 'Evidence summary: new medicine'.

Scottish Medicines Consortium (SMC) Policy Statement[16]

The SMC believes that the managed introduction of biosimilar medicines into clinical practice in NHS Scotland is desirable. To facilitate this process, from May 2015 the SMC will no longer routinely assess biosimilar medicines on the basis of a full submission. These products will be considered 'out of remit' where the reference product has been accepted by SMC/Health Improvement Scotland (HIS) for the same indication(s) and in the same population or was initially licensed and available prior to 31 January 2002.

Clinical evidence

The regulation of medicines in the European Union (EU) is overseen by the European Medicines Agency (EMA). Any new medicine wishing to become EU licensed must submit a package of evidence to the EMA for assessment. The recommended contents of a submission are laid out in specific guidelines relevant to the medicine concerned.[18] These guidelines include a specific document aimed at the development of biosimilar insulin products.[22]

The clinical development programme to show biosimilarity between Abasaglar and Lantus is based on five phase 1 and two phase 3 studies. The phase 1 studies primarily assessed pharmacokinetic parameters. Pharmacokinetic equivalence of the two insulins was convincingly demonstrated across all studies and all doses using methodology in line with CHMP guidance.[18] The two phase 3 clinical studies were conducted in patients with T1DM and T2DM.

Phase 1 studies

The pharmacokinetics (PK) and pharmacodynamics (PD) of Abasaglar and the EU- and US-approved versions of Lantus were evaluated in three phase 1, randomised, double-blind, cross-over replicate euglycemic clamp studies in healthy participants. Participants received 0.5U/kg doses of two different insulin glargine products on two separate occasions. Results showed similar PK and PD properties of Abasaglar® and Lantus.[23]

An additional phase 1, randomised, subject- and investigator-blinded study assessed the PK and PD of two other doses of Abasaglar® and Lantus (0.3 and 0.6 U/kg) in 24 healthy participants. Results were found to be similar between both products and were consistent across both administered doses.[24] Overall these phase 1 studies showed Abasaglar® and Lantus to have similar pharmacokinetic and pharmacodynamic profiles.[23,24]

Finally a phase 1 randomised, double-blind, crossover glucose clamp study assessed the duration of action of Abasaglar® and Lantus in 20 fasted males with type 1 diabetes. Results showed that the mean duration of action was 24 and 26 hours for Abasaglar® and Lantus, respectively.[25]

In all phase 1 studies Abasaglar® was well-tolerated, with no safety concerns noted in terms of adverse events, clinical laboratory tests, vital signs or ECG data. The frequency of adverse events reported was similar between the two treatments.[23-25]

Phase 3 studies

ELEMENT-1 was a 52-week, randomised, open-label study of 535 patients with T1DM. Patients in the study were also treated with mealtime insulin.[26]

ELEMENT-2 was a 24-week, randomised, double-blind study of 756 patients with T2DM inadequately controlled on two or more oral diabetes medicines.[27]

The primary objective in both studies was to evaluate whether Abasaglar® was non-inferior to Lantus in reducing average HbA1c levels from baseline at 24 weeks. In addition anti-insulin glargine antibodies were also measured to determine the immunogenicity profile of Abasaglar®.[28]

Patients with T1DM had HbA1c reductions of -0.4 % (Abasaglar®) and -0.5 % (Lantus) at 24 weeks, with similar results at 52 weeks.[26] Patients with T2DM had HbA1c reductions of -1.3 % in both insulin glargine treatment groups at 24 weeks.[27]

Approximately one-third of patients with T1DM reached target HbA1c levels of less than 7 % at 24 weeks with Abasaglar® (35 %) and Lantus (32 %) treatment (26). In patients with T2DM, approximately half of the patients reached these target levels with Abasaglar® (49 %) and Lantus (53 %) treatment.[27]

In both phase 3 studies each product led to significant decreases in average HbA1c levels. Neither product demonstrated non-inferiority to the other.[26,27]

In patients with T1DM the incidence of adverse events at 52 weeks was 62% for both products. The total average hypoglycaemia rate at 24 weeks was also similar between Abasaglar® and Lantus (87 and 89 events/patient/year, respectively).[26]

The frequency of adverse events was similar between the two treatments in patients with T2DM (52 % and 48 %, Abasaglar® and Lantus, respectively), including the total average hypoglycaemia rate (21 vs. 22 events/patient/year, Abasaglar® and Lantus, respectively).[27]

The phase 3 studies also evaluated whether both products led to similar development of insulin antibodies and similar effects of immune responses on clinical outcomes. Results showed a similar immunogenicity profile for the two products. Clinical outcomes, including HbA1c levels, basal insulin dose and total hypoglycaemia levels, were not affected by whether or not patients developed antibody response during the study.[28]

Costs and savings

The biosimilar product, Abasaglar®, is to be offered with a 15% discount versus the list price for Lantus. This means the prices for both products will be as follows:

Insulin glargine - Lantus

Injection, insulin glargine 100 units/mL, net price

- 10-mL vial = £30.68;
- 5 × 3-mL cartridge (for ClikSTAR ® and Autopen® 24) = £41.50;
- 5 × 3-mL Lantus ® SoloStar ® prefilled disposable injection devices = £41.50

Insulin glargine biosimilar - Abasaglar®

Injection, insulin glargine 100 units/ml, net price

- 5 x 3ml cartridge (for HumaPen Savvio) = £35.28
- 5 x 3ml disposable injection devices (for KwikPen) = £35.28

It is estimated using ePACT data that a one hundred per cent switch across England and Wales could save over £12 million. This equates to £19,926 per 100,000 patients. (ePACT data July - September 2015).

Summary

- There are now 18 biosimilar products approved and available for use within the EU, however Abasaglar® is the first biosimilar insulin to be launched. The regulatory authority in Europe, the EMA, have deemed Abasaglar® to have demonstrated the required high levels of quality, efficacy and safety in relation to the originator insulin product, Lantus.
- Biosimilars do typically reach the market with a lower acquisition cost compared to the originator and this is true of Abasaglar®. The discount of 15% makes initiation of biosimilar insulin glargine, in appropriate patients, an attractive proposition. There is also the potential to switch patients from Lantus to Abasaglar® where patients are agreeable. The manufacturers of Abasaglar® are not seeking to actively promote or support the switching of patients to their product. However if this savings opportunity is to be fully maximised then switching programmes may need to be implemented, where agreed, at a local level.

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Additional PrescQIPP resources

Briefing

Data pack

Available here: www.prescqipp.info/resources/viewcategory/430-biosimilars-insulin-analogues

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