PrescQIPP Community Interest Company

Biosimilars - Insulin glargine (Abasaglar®): A review of key issues and clinical concerns

A biological medicine, or biologic, is any medicinal product manufactured in, extracted from, or semi-synthesised from biological sources. Different from chemically synthesised pharmaceuticals, they include vaccines, blood components and recombinant therapeutic proteins.[1]

Insulin is one example from a wide range of biological medicines in use today. In the last ten years a number of biological medicines, including insulin glargine, have lost their patent protection within the European Union. This has enabled pharmaceutical companies to manufacture similar versions of these biologics and seek regulatory approval in Europe and other regions across the globe.

When a copy of a chemically synthesised molecule is produced the resulting product is termed a generic. However, when a biological medicine is successfully copied the result is a biosimilar. The reason for this difference in terminology is the complexity of the manufacturing process for biological medicines. This means that an exact copy cannot be produced i.e. it is deemed highly similar but not identical. This complexity means that the challenge of producing identical batches of biologics will equally elude manufacturers of branded medicines and biosimilars alike.

Biologic manufacture – It's complex

Biological medicines (and therefore biosimilars) vary widely in size and complexity. The human insulin molecule is a non-glycosylated, disulphide-bonded heterodimer containing 51 amino acids.[2] This makes it a relatively simple molecule when compared to other biological medicines e.g. infliximab, a monoclonal antibody, which contains 1328 amino acids.[3]

The manufacturing of biological medicine is inherently a complicated, multistep process.[4] First there is a process of targeting and cloning the desired DNA which is then transferred into a host cell expression system. The chosen cell line undergoes multiple stages of cell expansion, purification and validation before, finally, purified bulk drug is produced.

Storage and formulation of the final product can also potentially add additional variability. The final product will be reliant upon its primary and three-dimensional protein structure. Also vital will be the presence of any post-translational modifications, isoforms, aggregates, and impurities as well as excipients, and also any stabilizers used in the final pharmaceutical formulation. Any differences in the manufacturing process can result in a different product.[4]

What is a biosimilar?

A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine. A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the 'reference medicine'. Similarity to the reference medicine in terms of quality, structural characteristics, biological activity, safety and efficacy must be established. This is based on a comprehensive scientific comparability exercise. However, this process is not designed to show they are identical, merely highly similar. In the EU "Biosimilarity" is the regulatory term applied to a biosimilar shown to be "highly similar" to the reference product.[5]

The major challenge for a biosimilar product arises from the method of production selected because this will deliver a product that is not identical to the reference product. Even very small differences in the

copy version could impact on the efficacy and safety with respect to bioavailability, receptor binding, duration of action and adverse effects – including, for example, those related to differences in the immune response, antigenicity and antibody formation to an exogenous protein.[6]

In order to minimise any potential differences manufacturers must identify at each approval step any residual uncertainty about their product's biosimilarity and determine additional tests that would alleviate that uncertainty.[7] Should a manufacturer of biosimilars demonstrate that its product is highly similar to a reference product it will also be able to invoke the latter's efficacy, safety, and post-marketing data. Differences that may confer a safety advantage (e.g. lower levels of impurities) should be explained but are unlikely to preclude biosimilarity.[8]

However for a biosimilar to be approved it must demonstrate comparable efficacy. A product showing a greater, or lower, levels of efficacy, would not be deemed a biosimilar.[9,10]

How are biosimilar insulins regulated in the EU?

Manufacturers of biological medicines must completely describe their processes, including detailed and rigorous validation and monitoring of batch-to-batch variability - and especially the effect of any changes they may have introduced to the manufacturing process. The EMA requires manufacturers to regularly submit data that will fully describe the chemical manufacturing characteristics of their products. This will include detailed analysis of any raw materials utilised, reports on a wide range of in-process tests and extensive testing of each batch of final product produced.[11]

If a biopharmaceutical manufacturer makes any change to the established and verified manufacturing process then additional data is required to justify the amendment. This is termed a comparability exercise and depending on the scale of the process change will require additional analytical assessments or small scale clinical studies.[12]

The European Public Assessment Report (EPAR) document issued by the European Medicines Agency (EMA) for biosimilar insulin glargine (Abasaglar®) highlights the stringency with which the regulatory authorities evaluate a market approval dossier for a prospective biosimilar insulin, and details many of the issues that can arise.[13]

What is the regulatory process trying to prove?

The challenge for the regulators is to decide whether a biosimilar candidate has achieved "biosimilarity". The EMA regulators have set out in various guidelines how this can be achieved and there is a specific guideline in place for biosimilar insulins.[2]

There are five key elements to the approval process:

1. Analytical assessment - e.g. primary structure, purity, post-translational modifications.
2. Binding studies - e.g. to insulin receptors.
3. Biological activity - e.g. lipogenesis.
4. Non-clinical studies - e.g. pharmacokinetic and toxicity studies.
5. Clinical studies - e.g. phase 1 and 3 studies in specified indications.

The cornerstone of this approval process is the extensive comparison of the physicochemical and functional characteristics of the molecules using up-to-date analytical tools, i.e. stages 1-3 above.[14] This is because the high specificity of this technology means originators and biosimilars can be fully assessed and understood. If critical differences are detected, the impact on receptor binding and other functional mechanisms can be assessed. The function and performance of the biosimilar can then be assured before clinical studies.[15]

In the development of a biosimilar insulin the clinical studies have a different emphasis to that seen for the approval process for a novel insulin product. This is because demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles is considered the mainstay of proof of similar

efficacy of the biosimilar and the reference insulin. This proof is primarily provided via glucose clamp studies.

The glucose clamp technique is the standard method for determining the time and action profile of new insulin preparations, and the measurement of insulin and beta-cell sensitivity.[16] The EMA requires data on the time-action profiles of new insulin preparations, using the euglycaemic glucose clamp technique, for registration of new insulins in the treatment of diabetes mellitus.[17]

There is no anticipated need for specific efficacy studies with biosimilar insulins since endpoints used in such studies, e.g. HbA1c, are not considered sufficiently sensitive to show biosimilarity.[2] However two efficacy studies were also submitted by Lilly as part of the data package for Abasaglar®. From a regulatory perspective the purpose of these studies was to provide the safety and immunogenicity datasets required by the biosimilar insulin guideline.[13]

What clinical studies were undertaken for Abasaglar®?

Five phase 1 clinical studies were conducted. These were designed to establish PK and PD equivalence, for a range of dose levels, in healthy volunteers as well as in patients with type 1 diabetes.

In addition there were two phase 3 studies completed.[13]

- ELEMENT-1 was a 52-week, randomised, open-label study of 535 patients with type 1 diabetes.
- ELEMENT-2 was a 24-week, randomised, double-blind study of 756 patients with type 2 diabetes.

There has been considerable debate in the literature regarding the validity of glucose clamp studies in the regulation and approval of novel insulin products, particularly those with long durations of action, i.e. insulin glargine.[18] However when assessing biosimilar insulins the regulatory view is that PK and PD comparability forms the cornerstone on which biosimilarity is established. Glucodynamic studies using single subcutaneous doses of the test and reference agents are considered the most suitable method[13] and there is general agreement that this technique is the best available method for the measurement of insulin action.[2]

It is true that the duration of these clamp studies needs to take into account the known duration of action of the investigated insulin preparation and its dose-dependency. For long acting insulins, clamp durations of at least 24 hours are recommended with “Area Under the Curve” measures being the primary endpoint. When investigating novel insulins with duration of actions exceeding 24 hours this may present a limitation of clamp studies. However in the context of proving biosimilarity the primary issue is to demonstrate similar PK and PD profiles to the originator over the time course specified. In this case the data obtained was over the same 24 hour period that was specified for Lantus when it was seeking regulatory approval in 2005.[19]

The resulting data showed that the mean PK and PD curves were essentially superimposable.[20] The regulatory view was that PK and PD equivalence was convincingly demonstrated across all studies and all doses using methodology in line with the current guidance.[13]

Why are the outcomes of clinical efficacy studies not relevant?

The primary objectives of the two Phase 3 studies were to investigate how the PK and PD features of the biosimilar product translated into clinical parameters relevant for the management of patients with type 1 and 2 diabetes mellitus.

However in terms of demonstrating biosimilarity the regulators consider that the evaluation of HbA1c is not a sensitive endpoint and therefore efficacy studies evaluating HbA1c are not generally anticipated. It is the insensitivity of HbA1c to show statistically significant and clinically relevant difference between insulin types, as demonstrated by a number of studies of new insulins in the last 15 years that led the EMA to choose to place little reliance on clinical studies with HbA1c measurements for assessment of biosimilarity.[2]

However the two phase 3 studies did report on HbA1c levels in addition to a range of other parameters (including 7-point self-monitored blood glucose profiles and the data on intra-patient blood-glucose variability, basal and prandial insulin dose, and weight).

The results of these additional measures do not, in themselves, demonstrate biosimilarity; however they do constitute supportive evidence of clinical biosimilarity. A wide range of other potential measures have been suggested in the literature but in the context of proving biosimilarity they contribute little and would merely serve to satisfy academic curiosity.[21] So the most significant output of the phase 3 studies, from a regulatory perspective, was to provide the safety and immunogenicity datasets required for the biosimilar insulin.

Has the safety of biosimilar glargine been demonstrated?

For the specific EMA guidance relating to biosimilar insulins the main focus of any study gathering safety data is the adverse event profile.[21] This includes all events regardless of significance, e.g. hypoglycaemia, injection site tolerability. These are expected to remain within statistically defined limits of being indistinguishable for the biosimilar and the reference product.[2]

Demonstrating the safety of a biosimilar insulin does not have the same regulatory requirement as that for a novel insulin. The aim is to show comparable adverse event profiles over the most significant phase, in this case the first six months. If this can be demonstrated then long term safety will be assumed for the biosimilar. This is reflected by the same safety data being included within the Summary of Product Characteristics (SPC) for Lantus and Abasaglar®.[22,23]

A remaining question is: Are these relatively small studies with several hundreds of patients sufficient to demonstrate safety on a large scale?[14] Whilst this may be a valid point for a novel insulin where no historical safety data exists, it is less relevant for a biosimilar. In this situation the relatively short term (6-12 months) safety data is sought as further evidence of biosimilarity. If this has been demonstrated then large long-term studies are not required and would actually be of little value.[20]

The EMA concluded that the safety profile of Abasaglar® was well characterised in the context of the biosimilarity exercise. It appeared comparable to the safety profile of Lantus in the clinical studies and in line with the profile established and documented with the reference product. There were no major safety findings or signals identified in the clinical programme.[13]

The EMA assessment report for Abasaglar® also states that a Periodic Safety Update Reports (PSUR) will be submitted at pre-specified periods (typically six months for a newly launched product).[24]

PSURs are pharmacovigilance documents intended to provide a safety update resulting in an evaluation of the impact of the reports on the risk-benefit balance of a medicinal product. In addition a risk management plan is also included as part of the marketing authorisation detailing the required pharmacovigilance activities required post-launch.

Are there concerns about immunogenicity?

Early animal insulins were known to induce formation of insulin antibodies, often due to the presence of impurities that remained after the manufacturing process was complete.[14] Subsequently the invention of human insulins and high purification of insulin formulations has decreased the relevance of insulin antibodies to a large extent. Subcutaneous injection of human insulin does still induce some antibody formation (as is the case with other peptides), but without major consequences for efficacy or safety.[18,25]

As has been stated, analytics are the cornerstone of a biosimilar assessment process. However current laboratory and analytical methodologies are unable to evaluate the impact of any structural differences detected on immunogenicity. Consequently an analysis of the immunogenicity profile for any new biologic is a key function of the clinical studies undertaken, in this instance ELEMENT 1 and ELEMENT 2. These studies showed that the antibody profiles for Abasaglar and Lantus were comparable.

Why is there batch-to-batch variation?

Because of the complexity of the manufacturing process for a biopharmaceutical e.g. insulin, there will always be a degree of micro-heterogeneity between any batches produced.[16] This variability means that no two batches of any insulin will be identical and this applies as equally to originator products as it does to biosimilars.[26]

It is also true that even "minor" differences/changes in the manufacturing process could have considerable, and potentially clinically relevant, effects on the biological effects induced by an insulin.[25] In addition to changes of the insulin molecule, attention has also to be given to product related substances/impurities and process related impurities.[2] Again these concerns also apply to potential differences in originator insulins as they might result from manufacturing process changes.[27]

There is a clearly a drive for all pharmaceutical manufacturers to reduce their costs and maximise profitability. Maintaining the same level of production quality for every batch, and ensuring that good manufacturing practice is followed and documented, is undoubtedly costly.[25] These commercial pressures will clearly apply equally to manufacturers of originator products as well as biosimilars; however the need to achieve a consistently reliable product, via a robust manufacturing process, batch after batch is extremely important.

It is therefore highly reassuring to note that despite a rigorous monitoring, tracking, and tracing system, the EMA has identified no safety problems with any of the biosimilars launched to date in the EU.[28] This indicates that despite the financial pressures biosimilar manufacturers are continuing to maintain the high standards required for the on-going production, assessment and distribution of biosimilars within the EU.

How is batch to batch similarity assured?

Batch to batch variation applies equally to existing biologics and biosimilar medicines. Because of this there have been calls for greater transparency in relation to the potential variability between batches of approved insulin formulations.[27] The information on how manufacturers have to demonstrate to the regulators that they will maintain adequate batch-to-batch quality, and how they monitor it, is not in the public domain as it is commercially sensitive information.[20]

There have also been suggestions that the batch to batch variability of approved insulin formulations should be systematically investigated from a clinical point of view and that as more biosimilar insulins come to market, independent studies of batch-to-batch variability, and if possible clinical correlates, would be desirable.[20] Examples cited to support this view include clinical observations from Mexico and India that some copies of insulin glargine appear to have a dissimilar glycaemic effect.[29]

The requirement to perform a clinical assessment, i.e. utilising human volunteers, of every batch of a biological medicine produced would be extremely challenging from an operational perspective; in addition it would be financially prohibitive. More importantly the requirement for this level of clinical assessment of each batch is not required from a scientific or regulatory perspective. At the point at which a new biologic or biosimilar is launched the regulatory process has established the safety and efficacy of the final product and therefore all the manufacturing processes and steps involved in producing it. To do this the regulators will have overseen the detailed analysis of all raw materials, all in-process testing and the extensive requirements of the EPAR document required for submission of the final product. All subsequent batches will have to match up to the standards set for the first batch.

Should any manufacturing changes be introduced following product post-launch then the impact of this change will be assessed via an extensive comparability exercise. This will seek to establish whether the quality, safety and efficacy of the product are likely to have been affected in any way. If the outcome of this assessment is that the product still remains sufficiently "similar" then all subsequent batches will retain regulatory approval.

In the future it may become possible for analytical techniques to reliably predict safety and immunogenicity in humans. Until then we must continue to rely on the EMA regulatory procedures to protect patients from harm related to biological medicines as we have done for the last three decades.[6] Since biologics entered development the scientific progress of researchers in developing ever more effective and convenient insulins has been adequately matched by the implementation of high standards of quality control and a rigorous process of regulatory review.

What were the key findings of the EPAR?

The early quality assessments found the quality of the Abasaglar® to be acceptable and that comparability between the biosimilar and Lantus had been satisfactorily demonstrated from a quality perspective. The non-clinical assessments subsequently assessed the pharmacology, pharmacokinetics and toxicology of the biosimilar. There were not felt to be any non-clinical objections to the approval of Abasaglar®.

Next reported were the clinical studies and in particular the glucose clamp evaluations. Five separate studies utilised this method to assess PK and PD comparability and equivalence was established between the two products. The last section of the assessment dealt with the two phase 3 studies in type 1 and type 2 diabetes mellitus. Both studies demonstrated that the biosimilar was non-inferior to Lantus in achieving HbA1c levels and, therefore, provided strong supportive evidence regarding the comparability of the two products.

In addition, both studies provided data on patients switching from Lantus to the biosimilar at the same dose regimen; no difference in dose changes after titration to tighten glucose blood control was reported between the two treatment arms.

Lastly the safety profile for the biosimilar also appeared to be similar to that of Lantus and in line with the safety characteristics expected from an insulin product. No major safety findings or signals were identified and the antibody profiles for both products were comparable.[13]

On the basis of the data submitted, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of marketing authorisation subject to the submission of PSURs and a risk management plan, both of which are a standard requirement in this setting.

What does this mean for the NHS?

For health professionals within the NHS there are a range of issues to consider before initiating a patient on Abasaglar. These issues include the following:

a. Delivery device

For a patient receiving daily insulin injections the delivery device will be highly important. A patient's experience with their delivery device will be affected by perceived comfort and convenience. This is turn may affect adherence and ultimately outcomes.[30] All three main insulin manufacturers, Eli Lilly, Sanofi and Novo Nordisk, have sought to develop devices that enable less painful and more precise insulin administration.[31] Thus, the device through which a biosimilar insulin is administered may serve as a key market differentiator. However Abasaglar® is delivered in popular and widely accepted devices. In a survey of 442 insulin pen users, Eli Lilly's Lispro KwikPen received the highest satisfaction rating from among all pens used to deliver insulin analogues.[32]

Abasaglar was launched in the UK in September 2015. The SPC states that it will be available in pre-filled pens (KwikPen) and as cartridges.[22] The cartridges are delivered by the Savvio Humapen.

b. Initiation or substitution

Abasaglar is being promoted as an alternative to insulin glargine (Lantus) in patients deemed appropriate for a long-acting insulin analogue. The product is being sold at a 15% discount compared to the originator, Lantus. Savings achieved through initiation of the biosimilar will ultimately be significant

but will take time to achieve. A coordinated switching programme from Lantus to Abasaglar® would achieve more significant savings for local CCGs. However it would require patient consent as well as possible training for those unfamiliar with the Eli Lilly pen devices. In addition the manufacturers are not promoting, or supporting, the switching of patients established on Lantus to their biosimilar product.

Arguably the available discount may not be enough to encourage widespread switching and only further competition in this area will drive prices down further. However there is little prospect of that in the near future. At present no additional biosimilar insulin glargine products have been submitted to the EMA. Once a biosimilar is submitted the entire approval process takes between 12 to 18 months to complete.[13,33]

c. Brand name prescribing

As with all biosimilar products prescribing by brand name is strongly recommended.[34] 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.

d. National guidance

NICE has stated that they will not routinely produce a Health Technology Appraisal for all new biosimilar medicines. However 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.[35] Where required NICE will produce a Technology Appraisal Support for a new biosimilar product where necessary. This will be in a similar format to the one already produced for biosimilar infliximab.[36]

Summary

Ever since insulin analogues were first developed in the mid 90's, there has been a fierce discussion about the potential risks to patients posed by molecular changes introduced in the primary structure of the insulin analogues. These concerns have largely been negated with the passage of time and the generation of long term safety data.

We now seem to be entering a similar phase, in the EU and US, as a significant number of high cost biosimilar biopharmaceuticals approaches. Many of these biosimilars are more complex than Abasaglar but as this is the first biosimilar insulin approved by the EMA diabetologists are understandably wary on behalf of their patients.

However it is clear that the data package submitted by the Boehringer-Lilly Alliance for Abasaglar® gives a high probability of biosimilarity.[20] Based on this data package the CHMP considered that the risk-benefit balance of Abasaglar® in the treatment of diabetes mellitus in adults, adolescents and children aged over two years was favourable. They therefore recommended the granting of the required marketing authorisation.[13]

It is worth highlighting the extensive experience the EMA has in the regulation of biopharmaceuticals and biosimilars which stretches over three decades. In this time a robust and high quality regulatory framework has been established. In the last ten years this comprehensive framework has overseen the introduction, and subsequent monitoring, of 18 different biosimilar products within the EU. For this reason we can be reassured that the required standards of quality, safety and efficacy will be maintained with the introduction of the next product to be added to that list, biosimilar insulin glargine, namely Abasaglar®.

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