What are Biosimilar Medicines?

What are Biological medicines?

Biological medicines are medicines that are made or derived from a biological source and as such are complex, with inherent variability in their structure.[1]

They differ from a generic medicine, which contains simpler molecular structures. Generic medicines contain active ingredients that are identical to the originator medicine.[1]

What is a Biosimilar medicine?

Biosimilars are biological medicines that are highly similar in all essential aspects to a biological medicine that has already been authorised, known as reference product.[2] The biosimilar will have been shown not to have any clinically meaningful differences from the reference product in terms of quality, safety and efficacy.[5] After 10 years, once the exclusivity term of the reference medicine has expired, the biosimilar medicine is allowed to come out into the market.[2]

How are biosimilar medicines authorised for use?

In the European Union, Marketing Authorisation applications for biotechnology-derived medicines, including biosimilar medicines, are by law reviewed centrally by the European Medicines Agency.[1]

Once authorised by the European Commission, biosimilars are subject to the same level of post-authorisation regulatory scrutiny as reference products.[3] As of Brexit the procedure for approval in the UK is undertaken by the MHRA.[4]

For a biosimilar medicine to be approved, regulatory requirements include comprehensive comparability studies with the reference biological medicine. If a biosimilar is highly similar to a reference medicine and has comparable safety and efficacy in one indication, safety and efficacy data may be extrapolated to other indications already approved for the reference medicine, if scientifically justified. This avoids the unnecessary repetition of clinical trials.[1]

Where NICE has already recommended the originator biological medicine, the same guidance will apply to a biosimilar of that originator.[1]

Grace Vanterpool

Grace Vanterpool, Nurse Consultant in Diabetes at Diabetes Integrated Care Ealing summarised information on Biosimilar Medicines and here restates the key considerations when thinking of using a Biosimilar Insulin

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Why should the NHS use Biosimilar insulin?

Biological medicines are currently the largest cost and cost growth areas in the NHS medicines budget. Using a new commissioning framework, NHS England aims to drive a step change in the uptake of biosimilar medicines. Clinical commissioning groups commission hospital trusts to provide the treatment, and make sure patients are offered the choice of switching to a new product by their specialist hospital doctor. Through making biosimilar medicines more quickly available the NHS will be able to take advantage of savings each year offered by these new products, enabling more patients to have access to other lifesaving and life-enhancing treatments.[5]

Can a patient already established on insulin be switched to a biosimilar insulin?

Patients can be switched to a biosimilar medicine at the discretion of the prescriber in consultation with the patient, with appropriate monitoring in place. There is also growing practical NHS experience that demonstrates the safety and efficacy of biosimilars in clinical practice. Biosimilar products are considered to be interchangeable with their reference product, which means a prescriber can choose the biosimilar medicine over the reference product (or vice versa) and expect to achieve the same clinical effect or therapeutic equivalence. This decision rests with the prescriber in consultation with the patient in line with the principles of shared decision making.[1]

Can the Biosimilar insulins be substituted?

Substitution is not permitted for biological medicines, including biosimilars. In line with MHRA guidance all biological medicines, including biosimilars, should be prescribed by brand name.[1]

As biosimilar medicines often use the same international non-proprietary name as their reference product, an important way to ensure substitution does not take place is through brand name prescribing.[1] Brand name prescribing should be adhered to by all prescribers of biological medicines, including biosimilars, and is in line with recommendations and advice from MHRA and NICE, as well as being enshrined in EU law.[1] The insulins may be similar but the delivery devices will differ, for those insulins available in cartridge form the cartridges are not transferrable between different pens.[6]

Key considerations when using a Biosimilar Insulin

- The changes to insulin regimens should only be made by the health care professional with relevant expertise and training.
- The decision regarding which insulin is most appropriate should always be made jointly between the person with diabetes and their health care professional.
- Prescribers should include the brand name of the medicine in the prescription to avoid prescribing errors.
- People established on insulin who are achieving the HbA1c targets and who do not have hypoglycaemia should not be automatically switched to a biosimilar insulin.
- Adverse reactions to a biosimilar insulin should be reported to the MHRA so that the appropriate monitoring can take place.
- Health care professionals must keep their knowledge of available insulin up to date.
- Biosimilars are similar but not identical and are not direct equivalents of reference medicines in the same way that generics are equivalent to branded medicines.

REF: Bartha,K Guidelines for Nurses Expert Articles A top tips guide to biosimilar insulins 2019 July. Available at https://www.guidelines.co.uk/expert-articles/a-top-tipsguide-to-biosimilar-insulins/455381.article (accessed April 2023)

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References

1. NHS England what is a biosimilar medicine? May2019 https://www.england.nhs.uk/wp-content/uploads/2019/05/what-is-a-biosimilar-medicine-guide-v2.pdf (accessed April 2023)

2. EMA, Biosimilar medicines: marketing authorization. 2019. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation#1.-eligibility-and-reference-product-section (accessed April 2023)

3. European Commission: Medicinal Products https://ec.europa.eu/health/human-use_en (accessed April 2023)

GOV.UK: Guidance on licensing biosimilars, ATMPs and PMFs. https://www.gov.uk/guidance/guidance-on-licensing-biosimilars-atmps-and-pmfs (accessed April 2023)

4. NHS England. Biosimilar medicines. www.england.nhs.uk/medicines/biosimilar-medicines/ (accessed April 2023)

5. Association of British Clinical Diabetologists. Association of British Clinical Diabetologists (ABCD) position statement on the use of biosimilar insulin. BJD 2018; 18 (4): 171–174.

Prescribing Information:

Admelog (Insulin lispro 100 units/ml)
Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentations: Admelog 100 units/ml solution for injection in a vial, each containing 10ml of solution for injection, equivalent to 1000 units. Admelog 100 units/ml solution for injection in a cartridge or in a pre-filled pen each containing 3 ml of solution for injection, equivalent to 300 units insulin lispro.

Indication: For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis and for the initial stabilisation of diabetes mellitus.

Dosage and Administrations: The dose should be determined by the physician, according to the requirement of the patient. Admelog may be given shortly before meals, when necessary can be given soon after meals. Insulin lispro takes effect rapidly and has a shorter duration of activity (2-5 hours) given subcutaneously as compared with regular insulin, regardless of injection site. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual and duration of action is dependent on dose, site of injection, blood supply, temperature, and physical activity. Admelog can be used in conjunction with longer-acting insulin or oral sulphonylurea medicinal products, on the advice of a physician. Admelog in cartridges are only suitable for subcutaneous injections from a reusable pen. Admelog in pre-filled pen are only suitable for subcutaneous injections. Admelog solution for injection should be given by subcutaneous injection or by continuous subcutaneous infusion pump and may, although not recommended, also be given by intramuscular injection. If necessary, it may also be administered intravenously. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used. *Subcutaneous administration:* Should be in the upper arms, thighs, buttocks, or abdomen. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Care should be taken when injecting to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use the proper injection techniques. *Administration via an insulin infusion pump (Admelog vials only):* Admelog should not be mixed with any other insulin. Continuous subcutaneous insulin infusion (CSII) may be given in pump systems suitable for insulin infusion; only certain CE-marked insulin infusion pumps may be used. Before infusing, the manufacturer's instructions should be studied to ascertain the suitability or otherwise for the particular pump. Use the correct reservoir and catheter for the pump. The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set. A pump malfunction or obstruction of the infusion set can result in a rapid rise in glucose levels. If an interruption to insulin flow is suspected, follow the instructions in the product literature. *Intravenous administration (Admelog vials only):* Should be carried out following normal clinical practice for intravenous injections; frequent monitoring of the blood glucose levels is required. **Special Populations:** *Renal/Hepatic impairment:* Insulin requirements may be reduced. Patients with chronic hepatic impairment may have diminished insulin sensitivity and therefore require an increased dose. *Paediatric population:* Admelog can be used in adolescents and children.

Contraindications: Hypoglycaemia, hypersensitivity to insulin lispro or to any of the excipients.

Precautions and Warnings: *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. *Transferring to another type/ brand of insulin:* Should be done under strict medical supervision and may result in the need for change in dose. For fast-acting insulins, any patient also on basal insulin must optimise dose of both insulins to obtain glucose control across the whole day, particularly nocturnal/fasting glucose control. *Injection technique:* Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered. *Hypoglycaemia or hyperglycaemia:* Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease or medications such as beta-blockers. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death. Inadequate dose or discontinuation of treatment, especially in insulin dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal. *Dose adjustment:* Insulin requirements may be increased during illness or emotional disturbances. Adjustment of dose may also be necessary if patients undertake increased physical activity or change their usual diet. *In combination with pioglitazone:* Cases of cardiac failure have been reported, especially in patients with risk factors for development of heart failure. Patients using this combination should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. *Medication errors:* Patients must be instructed to always check the insulin label before each injection to avoid mix-ups between Admelog and other insulin products. Patients must visually verify the dialled units on the dose counter of the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device. *Excipients:* This medicine is essentially "sodium-free". *Pregnancy:* It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes. *Breastfeeding:* Patient may require adjustments in insulin dose, diet or both.

Interactions: The physician should be consulted when using other medicinal products in addition to Admelog. Insulin requirements may be increased by medicinal products with hyperglycaemic activity and reduced in the presence of medicinal products with hypoglycaemic activity.

Adverse Reactions: Hypoglycaemia is the most frequent adverse reaction. Oedema has been reported, particularly if previous poor metabolic control is improved by intensified insulin therapy. *Common (≥1/100 to <1/10):* Local allergy. *Uncommon (≥1/1,000 to <1/100):* Lipodystrophy. *Rare (≥1/10,000 to <1/1,000):* Systemic allergy. *Not known (cannot be estimated from the available data):* Cutaneous amyloidosis. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM.

Marketing Authorisation (MA) Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

UK List price and MA Numbers: *Admelog 100 units/ml solution for injection in vial 1 x 10ml:* £14.12 – PLGB 04425/0822. *Admelog 100 units/ml solution for injection in cartridge 5x 3ml:* £21.23 – PLGB 04425/0823. *Admelog 100 units/ml solution for injection in pre-filled pen 5 x 3ml:* £22.10 – PLGB 04425/0824.

Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. uk-medicalinformation@sanofi.com.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Sanofi Tel: 0800 090 2314. Alternatively, send via email to UK-drugsafety@sanofi.com

Prescribing Information:

Trurapi ▼ (Insulin aspart 100 units/ml)

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Presentation: Trurapi 100 units/ml (equivalent to 3.5 mg) solution for injection in a vial, each containing 10ml of solution for injection, equivalent to 1000 units. Trurapi 100 units/ml solution for injection in a cartridge or in a pre-filled pen, each containing 3ml of solution for injection, equivalent to 300 units insulin aspart.

Indication: The treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

Dosage and Administration: Trurapi is a rapid-acting insulin analogue, normally used in combination with intermediate-acting or long-acting insulin. Trurapi should not be mixed with any other insulin. The dosage should be determined by the physician in accordance with individual patient needs. Blood glucose monitoring and insulin dose adjustments are recommended to achieve optimal glycaemic control. The individual insulin requirement in adults and children is usually 0.5–1.0 unit/kg/day. In a basal-bolus treatment regimen 50–70% of this requirement may be provided by Trurapi and the remainder by intermediate-acting or long-acting insulin. Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness (see Precautions and Warnings). *Transfer from other insulin medicinal products:* When transferring from other insulin medicinal products, adjustment of the Trurapi and basal insulin dose may be necessary as Trurapi has a faster onset and a shorter duration of action than soluble human insulin. When injected subcutaneously into the abdominal wall, the onset of action will occur within 10–20 minutes of injection. The maximum effect is exerted 1–3 hours after the injection with duration of action of 3–5 hours. Subcutaneous administration: This should be in the upper arms, thighs, buttocks or abdomen and injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Subcutaneous injection in the abdominal wall ensures a faster absorption than other injection sites and faster onset of action of insulin aspart is maintained regardless of the injection site. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity. Due to the faster onset of action, insulin aspart should generally be given immediately before a meal. When necessary insulin aspart can be given soon after a meal. *Trurapi in cartridges:* only suitable for subcutaneous injections from a specified type of reusable pen. *Trurapi in pre-filled pen:* only suitable for subcutaneous injections. Trurapi in pre-filled pen delivers 1-80 units in increments of 1 unit. Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device. Administration via an insulin infusion pump (Trurapi vials only): CSII should be administered in the abdominal wall and infusion sites should be rotated. Patients using CSII should be comprehensively instructed in the use of the pump system and use the correct reservoir and tubing for the pump. The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set. An alternative insulin delivery method should be available in case of pump system failure. Intravenous administration (Trurapi vials only): This should be carried out by physicians or other healthcare staff following normal clinical practice for intravenous injections. Monitoring of blood glucose is necessary during insulin infusion.

Special Populations: Elderly patients (≥ 65 years old) and renal/hepatic impairment: Trurapi can be used in elderly patients and patients with renal or hepatic impariment; glucose monitoring should be intensified and dose adjusted on an individual basis. Paediatric population: Trurapi can be used in adolescents and children aged 1 year and above in preference to soluble human insulin when a rapid onset of action might be beneficial, for example, in the timing of the injections in relation to meals. The safety and efficacy in children below 1 year of age have not been established.

Contraindications: Hypersensitivity to insulin aspart or to any of the excipients.

Precautions and Warnings: Traceability: The name and the batch number of the administered product should be clearly recorded to improve the traceability. Injection technique: Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medicinal products may be considered. Hyperglycaemia: Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia: Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Especially in children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose level in order to minimise the risk of hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement and in case of hypoglycaemia or if hypoglycaemia is suspected insulin aspart must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered. Patients whose blood glucose control is greatly improved may experience a change in their usual warning symptoms of hypoglycaemia, and usual warning symptoms may disappear in patients with longstanding diabetes, so patients should be advised accordingly. Hypoglycaemia in rapid-acting insulin analogues may occur earlier after an injection when compared with soluble human insulin and since insulin aspart should be administered immediately in relation to a meal, the rapid onset should be considered in patients with concomitant diseases or treatment where a delayed absorption of food might be expected. Concomitant illness usually increases the patient's insulin requirements and concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose. When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin. Transfer from other insulin medicinal products: Should be done under strict medical supervision. If dose adjustment is needed, it may occur with the first dose or during the first few weeks or months. Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter. Injection site reactions (including lipodystrophy and cutaneous amyloidosis): As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions and these usually resolve in a few days to a few weeks. Continuous rotation of the injection site also reduces the risk of developing lipodystrophy and cutaneous amyloidosis. Blood glucose monitoring is recommended after the change in the injection site due to risk of hypoglycaemia, and dose adjustment of antidiabetic medications may be considered. On rare occasions, injection site reactions may require discontinuation of insulin aspart. Combination with pioglitazone: Cases of

cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Medication errors: Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Trurapi and other insulin medicinal products. Insulin antibodies: Insulin administration may cause insulin antibodies to form, which in rare cases may necessitate adjustment of the insulin dose to correct a tendency to hyper- or hypoglycaemia. Travel: Patients should seek physician advice before travelling to different time zones as this may mean that the insulin and meals may be taken at different times. Sodium: This medicinal product contains less than 1 mmol sodium (23mg) per dose, that is to say essentially "sodium free". **Interactions:** Several medicinal products are known to interact with the glucose metabolism. Substances that may reduce insulin requirements: Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides. Substances that may increase insulin requirements: Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol. Other potential interactions of note: Octreotide/lanreotide may either increase or decrease the insulin requirement. Beta-blockers may mask the symptoms of hypoglycaemia. Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Pregnancy and Breast-Feeding: Pregnancy: It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy and intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Data from two randomised controlled clinical trials do not indicate any adverse reaction of insulin aspart on pregnancy or on the health of the fetus/newborn when compared to human insulin. Breast-feeding: There are no restrictions on treatment with Trurapi during breast-feeding, but the dose may need to be adjusted.

Adverse Reactions: Adverse reactions observed in patients using Trurapi are mainly due to the pharmacologic effect of insulin. Hypoglycaemia is the most frequent adverse reaction and may occur if the insulin dose is too high in relation to the insulin requirement. *Uncommon (≥1/1,000 to <1/100):* urticaria, rash, eruptions, refraction disorders, diabetic retinopathy, injection site reactions such as lipodystrophy and oedema that can be reduced by continuous rotation of the injection site. *Rare (≥1/10,000 to <1/1,000):* Peripheral neuropathy (painful neuropathy). *Very rare (<1/10,000):* anaphylactic reactions which can potentially be life threatening. *Frequency not known:* cutaneous amyloidosis. Special populations: The frequency, type and severity of adverse reactions observed in the paediatric population, elderly patients and patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population. *Prescribers should consult the SPC in relation to other adverse reactions.*

Legal Category: POM

Marketing Authorisation (MA) Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.

GB List price and MA numbers: *Trurapi 100 units/ml solution for injection in vial 1 x 10ml:* £11.97 – PLGB 04425/0891. *Trurapi 100 units/ml solution for injection in cartridge 5 x 3ml:* £19.82 – PLGB 04425/0885. *Trurapi 100 units/ml solution for injection in pre-filled pen 5 x 3ml:* £21.42 – PLGB 04425/0886.

Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. uk-medicalinformation@sanofi.com. **SmPC Date:** 29/03/2023

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