NHS Bedfordshire Clinical Commissioning Group

NHS Luton Clinical Commissioning Group

Bedfordshire and Luton Joint Prescribing Committee

June 2016

Review June 2019

Bulletin 240 - High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error – Safety Reminder

JPC Recommendations:

At the April 2016 JPC meeting, ongoing safety concerns relating to the use of high strength and biosimilar insulin products in both primary and secondary care were highlighted. As a result of this, it was agreed that a short paper would be produced to remind health care professionals of these concerns and provide advice to minimise the risk. This bulletin/review focuses on safety and does not specifically endorse the use of these products. Use must be initiated and supervised by the specialist team.

Advice for healthcare professionals:

Before starting treatment with a high strength, fixed combination or biosimilar insulin product:

- consult the summary of product characteristics and any educational material – see below
- always prescribe by brand and the insulin dose in units ("units" to be spelled out and stated in lower case) and include the dose frequency. The strength of the insulin formulation should also be always included in the prescription and a statement of the formulation (e.g. cartridge or disposable pen)
- 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) – see below
- warn patients only to use insulin as they have been trained 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.

Additional advice for healthcare professionals on the use of high-strength insulin:-

• The insulin is supplied in a pre-filled pen and it should only be used with this device. **Healthcare professionals must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose can result.**

• When switching patients from standard-strength insulin to an insulin formulation that is **not bioequivalent** (such as Toujeo, insulin glargine 300 units/ml), switching can be done on a unit to

unit basis, but the dose may need to be adjusted to achieve target ranges for plasma glucose level. More detailed information on such dose adjustment is provided in the product information.

• Explain differences in the design of the package and the pre-filled pen for high-strength insulins and standard-strength insulins, especially if the patient has been transferred from standard-strength insulin to high-strength insulin. Focus on colour differentiation, warning statements on carton/label and other safety design features (such as tactile elements on the pre-filled pen).

• If different short-and long-acting insulins are being prescribed together, the differences in appearance and use between the two pen devices must be highlighted.

• Pharmacists should be aware that insulins are now available in different strengths.

• Pharmacists are encouraged to check that patients and carers are able to read the strength of insulin and the dose counter of the pen device before dispensing the medicine. Pharmacists should also check that patients have been trained on how to use the new pen.

• Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using the insulin pen device.
In addition, healthcare professionals are encouraged to take the following precautions when storing and dispensing high strength insulins:
• Ensure that electronic and paper systems used to prescribe and dispense these medicines facilitate correct selection of the medicine and avoid confusion with other medicines.

• Always carefully check the product selected in electronic prescribing or dispensing systems.

• Ensure that storage arrangements for combination insulin medicines facilitate correct selection of the medicine and avoid confusion with other medicines.

Links to key Further Information:
The information used to inform these recommendations is largely based on the information contained in appendices 1 and 2.

NB: Links to the relevant documents have been added below. In the event of a technical error, if these do not work, please copy and paste the web address into a web browser and search for the relevant document.

Draft guidance - High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error, Drug Safety Update, April 2015
www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error **(Appendix 1)**

Guidance on prevention of medication errors with high-strength insulins issued by the European Medicines Agency in November 2015

www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500197133 **(Appendix 2)**

In Use Product Safety Assessment Report for Toujeo® and Abasaglar®, UKMi, October 2015.
www.ukmi.nhs.uk/filestore/ukmiaps/InsulinglarginesOct-2015_1.pdf

Toujeo guidance for healthcare professionals April 2015

Toujeo guidance for patients and carers April 2015

Letter on insulin lispro (Humalog 200 units/mL KwikPen): correct use to minimise medication errors, sent to healthcare professionals in March 2016

Letter on Tresiba sent to healthcare professionals in January 2013

Drug Safety Update article on reducing risk of medication error with Tresiba

Xultophy summary of product characteristics

Abasaglar summary of product characteristics

Adult insulin passport

Patient information booklet

http://www.evidence.nhs.uk/formulary/bnf/current

Appendix 1

Draft guidance - High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error, Drug Safety Update, April 2015

https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error

Several new high strength insulin products are now on the market. The European Medicines Agency is consulting on guidance to minimise the risk of medication error.

1. Public consultation
2. Overview of products on the market
3. High strength insulin products
    1. The dose step
    2. Dose conversion when switching between standard and high strength insulin products
4. Xultophy▼: insulin in fixed combination with liraglutide
5. Abasaglar▼: biosimilar insulin
6. Further information

Public consultation

It is likely that further such insulin products will come to market over the next few years. This draft guidance summarises ways to minimise the risk of medication errors with high strength, fixed combination and biosimilar insulin products already on the market. We encourage you to comment on the risk minimisation strategy for high strength and fixed combination insulin products which is being developed by the European Medicines Agency. The consultation is open until 14 June 2015.

Overview of products on the market

Several new insulin products have come to market recently; three high strength insulins which have concentrations greater than 100 units/mL (Tresiba▼, Humalog, Toujeo), a fixed combination of insulin degludec and liraglutide (Xultophy▼) and a biosimilar of insulin glargine (Abasaglar▼).

Details of the new products are as follows:

Key feature	Active substance	Brand name	Strengths available (units/mL)	Administration device
High strength	Insulin degludec	Tresiba▼	100	FlexTouch prefilled pen; cartridge ('Penfill' for use in Novo Nordisk reusable pen)
			200	FlexTouch prefilled pen
	Insulin lispro	Humalog	100	KwikPen prefilled pen; vial; cartridge (for *Autopen® Classic* or *HumaPen®*)
			200	KwikPen prefilled pen
	Insulin glargine	Lantus	100	SoloStar prefilled pen; vial; cartridge(for *ClikSTAR®* and *Autopen® 24*) ;
		Toujeo ▼	300	SoloStar prefilled pen
Fixed combination	Insulin degludec and liraglutide	Xultophy▼	100 units/mL of insulin degludec and 3.6 mg/mL of liraglutide	Prefilled pen
Biosimilar	Insulin glargine	Abasaglar▼	100	KwikPen prefilled pen; cartridge (for use in Lilly reusable pen)

Healthcare professionals and patients need to understand the insulin strength of these products and how to use them correctly to minimise the risk of medication errors such as the wrong insulin dose being administered.

Details on the correct use of these products are given in the further information below.

High strength insulin products

High strength insulin products have been developed for patients with large daily insulin requirements to reduce the number and volume of injections.

The dose step

The ‘dose step’ is a new term to define how patients dial up the required drug dose on the prefilled pen.

For Lantus, Toujeo and both strengths of Humalog:

- one dose step on the prefilled pen is equivalent to one unit of insulin.

In contrast, with Tresiba:

- one dose step on the 100 units/mL pen is equivalent to one unit of Tresiba
- one dose step on the 200 units/mL pen is equivalent to 2 units of Tresiba

For further information on reducing risk of medication error with Tresiba, see the April 2013 Drug Safety Update article on Tresiba, the letter on Tresiba sent to healthcare professionals, and the Tresiba summary of product characteristics.

Dose conversion when switching between standard and high strength insulin products

For all the insulin products in the table above, the required dose is displayed in the dose counter window of the prefilled pen.

For Humalog 100 and 200 units/mL KwikPens, and for Tresiba 100 and 200 units/mL FlexTouch pens:

- there is **no need for dose conversion** when transferring patients from the standard to high strength version or vice versa.

However, Toujeo is **not bioequivalent** to Lantus:

- dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa - for dose conversion instructions, see the Toujeo guidance for healthcare professionals.

Xultophy▼: insulin in fixed combination with liraglutide

Xultophy is the first product to combine insulin with another injectable treatment; it combines insulin degludec 100 units/mL with liraglutide 3.6 mg/mL in a prefilled pen. Liraglutide (Victoza) is a glucagon-like peptide-1 (GLP-1) receptor agonist licensed for the treatment of type 2 diabetes. One dose step on the Xultophy prefilled pen is equivalent to one unit of insulin degludec and 0.036 mg of liraglutide. For further information, see the Xultophy summary of product characteristics.

Abasaglar▼: biosimilar insulin

Abasaglar is a biosimilar medicine based on insulin glargine 100 units/mL (Lantus) and is licensed for the treatment of diabetes in adults, adolescents, and children aged 2 years and above. Abasaglar has been shown to be equivalent to Lantus in its pharmacokinetic and pharmacodynamic properties. However, as with other biosimilar medicines, some dose adjustment may be needed for some patients. For further information, see the Abasaglar summary of product characteristics.

Advice for healthcare professionals:

Before starting treatment with a high strength, fixed combination or biosimilar insulin product:

- consult the summary of product characteristics and any educational material – see below
- 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) – see below
- warn patients only to use insulin as they have been trained 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.

Further information

Toujeo guidance for healthcare professionals April 2015

Toujeo guidance for patients and carers April 2015

Letter on Humalog sent to healthcare professionals on 16 February 2015

Letter on Tresiba sent to healthcare professionals in January 2013

Drug Safety Update article on reducing risk of medication error with Tresiba

Xultophy summary of product characteristics

Abasaglar summary of product characteristics

Adult insulin passport

Patient information booklet

Article citation: Drug Safety Update volume 8 issue 9 April 2015:

Appendix 2

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 November 2015
EMA/134145/2015

Guidance on prevention of medication errors with high-strength insulins

A high-strength insulin is a medicine that contains insulin at a concentration of more than the standard 100 units/ml, which for many years has been the only strength available across the EU. Medicines containing high-strength insulin may allow patients to receive a high dose in a single injection, and help meet an increasing need for higher doses of insulin. However, there are differences in the way high-strength insulin products are used compared with existing insulin formulations of standard-strength and there is therefore a risk of medication errors and accidental mix-ups.

Patients and healthcare professionals are therefore advised to take extra care when using high-strength insulin medicines and to carefully follow the recommendations given below.

Recommendations for patients and carers

- If the concentration of insulin stated on your medicine pack is **higher than 100 units/ml**, you are using high-strength insulin. Read the instructions in your package leaflet carefully before using this medicine.
- If you are using other types of insulin alongside your high-strength insulin, always check the strength on the packaging and the label of each type of insulin before every injection to avoid mixing them up.
- The high-strength insulin is supplied in a pre-filled pen and it should only be used with this device. The dose counter of the pen device displays the number of units of insulin irrespective of strength.
- If you are being transferred from standard-strength insulin to a high-strength insulin you will usually be using the same number of units that you were when using the standard-strength insulin.[1] This also applies if you are being transferred from a high-strength to a standard-strength insulin. Always follow the instructions of your healthcare professional.
- If you are being transferred from standard strength insulin to high-strength insulin, your healthcare professional will highlight any differences in design between your high-strength insulin pen and other standard-strength insulin pens.
- You must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose may result.

[1] In exceptional cases your dose may need to be changed because of differences in the way the high-strength and standard strength solutions are taken up into the body – your doctor will advise you if this is needed.

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- During the switch to high-strength insulin and in the weeks after the switch you should measure your blood sugar levels more frequently.
- If you have any questions speak to your healthcare professional.

Recommendations for healthcare professionals

- Ensure that your patients are adequately informed on how to use their high-strength insulin.
- The insulin is supplied in a pre-filled pen and it should only be used with this device. Healthcare professionals must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose can result.
- When switching patients from standard-strength insulin to an insulin formulation that is **not bioequivalent** (such as Toujeo, insulin glargine 300 units/ml), switching can be done on a unit to unit basis, but the dose may need to be adjusted to achieve target ranges for plasma glucose level. More detailed information on such dose adjustment is provided in the product information.
- Tell patients to closely monitor their blood sugar levels when starting high-strength insulin and in the weeks after.
- Always prescribe the insulin dose in units ("units" to be spelled out and stated in lower case) and include the dose frequency. The strength of the insulin formulation should also be always included in the prescription.
- Explain differences in the design of the package and the pre-filled pen for high-strength insulins and standard-strength insulins, especially if the patient has been transferred from standard-strength insulin to high-strength insulin. Focus on colour differentiation, warning statements on carton/label and other safety design features (such as tactile elements on the pre-filled pen).
- If different short-and long-acting insulins are being prescribed together, the differences in appearance and use between the two pen devices must be highlighted.
- Pharmacists should be aware that insulins are now available in different strengths.
- Pharmacists are encouraged to check that patients and carers are able to read the strength of insulin and the dose counter of the pen device before dispensing the medicine. Pharmacists should also check that patients have been trained on how to use the new pen.
- Patients who are blind or with poor vision must be instructed to always get assistance from another person who has good vision and is trained in using the insulin pen device.

In addition, healthcare professionals are encouraged to take the following precautions when storing and dispensing high strength insulins:

- Ensure that electronic and paper systems used to prescribe and dispense these medicines facilitate correct selection of the medicine and avoid confusion with other medicines.
- Always carefully check the product selected in electronic prescribing or dispensing systems.
- Ensure that storage arrangements for combination insulin medicines facilitate correct selection of the medicine and avoid confusion with other medicines.

More information

Examples of high-strength insulin formulations are Tresiba (200 units/ml insulin degludec) and Humalog (insulin lispro 200 units/ml).

Toujeo (insulin glargine 300 units/ml), although it is also a high-strength insulin, is not bioequivalent to insulin glargine 100 units/ml (such as Lantus) which means that these insulins are not interchangeable. Therefore, when switching from insulin glargine 100 units/ml to Toujeo, this can be done on a unit to unit basis, but a higher Toujeo dose (approx. 10-18%) may be needed to achieve target ranges for plasma glucose level.

Further information on the safe use of these medicines and other ways to minimise the possible risk of medication errors with these medicines can be found in the guidance on risk minimisation strategies for high-strength and fixed-combination insulin products.