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Medicines Optimisation

High Strength, Fixed Combination and Biosimilar Insulin Products: Minimising the Risk of Medication Error

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1. Executive Summary

A number of new insulin products have recently come to the UK market:

- three high strength insulins which have concentrations greater than 100 units/mL:
    - Insulin degludec 200 units/ml (Tresiba)
    - Insulin lispro 200 units/ml (Humalog)
    - Insulin glargine 300 units/ml (Toujeo)
- a biosimilar insulin
    - Insulin glargine 100 units/mL biosimilar (Abasaglar) – launched August 2015
- a fixed combination of insulin with another medicine
    - insulin degludec 100 units/ml with liraglutide 3.6 mg/ml (Xultophy)

This document summarises the current guidance and recommendations on ways to minimise the risk of medication errors with these preparations.

Also available as an unlicensed medicine in the UK is Humulin R U-500, containing 500units/ml. It is usually classed as a red drug (secondary care specialist only) in the UK and can be prescribed only on a named patient basis for use in a very small number of insulin resistant patients who require very high doses.

1.1. Purpose of briefing

Healthcare professionals need to be aware of the possible risks of medication error following the introduction of several high strength insulin products, some of which are in combination with other medicines, or are biosimilar medicines based on insulin glargine.

Among the key recommendations from the Medicines and Healthcare Product Regulatory Agency (MHRA)[1], the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC)[2] *and* the UK Medicines Information Centre (UKMIi)[3] *publications, there are issues around prescribing and medicines use which are of relevance to prescribers (particularly those running diabetes clinics) and to community and hospital pharmacists. The key issues are detailed in the document below:*

2. Background

Several new insulin products are now on the market and it is likely that more new products will come to market over the next few years. There are differences in the way these products are used compared with existing formulations, and therefore there is a risk of medication errors if not used as recommended. There is a potential risk of accidental mix-ups with existing insulin formulations of standard strength.

The "April 2015 MHRA Drug Safety Update"[4] summarised ways to minimise the risk of medication errors with high strength, fixed combination and biosimilar insulin products. Concerns regarding potential medication errors were also raised by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC)[5].

They published their risk minimisation strategy for high strength and fixed combination insulin products in October 2015. Also in October 2015, the UK Medicines Information Centre (UKMi)[6] produced a safety assessment report for Toujeo and Abasaglar (insulin glargine).

2.1. Key Message

Healthcare professionals need to understand and be able to explain the key safety elements concerning these products and how to prescribe and use them correctly, to minimise the risk of medication errors such as the wrong insulin formulation, device, or dose being prescribed, dispensed or administered.

It is best practice to provide patients with a patient information booklet and an Insulin Passport[7] to help provide accurate identification of their current insulin products and provide essential information across healthcare sectors.

2.2. 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▼)
- a **biosimilar** of insulin glargine (Abasaglar▼)

The place in therapy and formulary position of these products is determined by each locality's decision making process. Details of the new products (and existing licensed high strength insulin products) are shown below:

Key feature	Active substance	Brand name	Strengths available	Administration devices
High strength insulin	Insulin degludec	Tresiba▼	100 units/ml	FlexTouch prefilled pen, cartridge
			200 units/ml	FlexTouch prefilled pen
	Insulin lispro	Humalog	100 units/ml	KwikPen prefilled pen, cartridge, vial
			200 units/ml	KwikPen prefilled pen
	Insulin glargine	Lantus	100 units/ml	SoloStar prefilled pen, vial, cartridge
		Touejo▼	300 units/ml	SoloStar prefilled pen
Fixed combination of insulin and liraglutide	Insulin degludec and liraglutide	Xultophy▼	100 units/mL of insulin degludec and 3.6 mg/mL of liraglutide	Prefilled pen
Biosimilar insulin	Insulin glargine	Abasaglar▼	100 units/mL	KwikPen prefilled pen, cartridge

The UKMi In Use Product Safety Asessment Report for Toujeo and Abasaglar[8] contains product photos of Touejeo Abasaglar and Lantus.

3. High Strength Insulins

3.1. How to use the high strength insulin products

High strength insulin products have been developed for patients with large daily insulin requirements with the aim of reducing the number and/or volume of injections.

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

For Lantus (glargine), Toujeo (glargine) and both strengths of Humalog (lispro):

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

In contrast, with Tresiba (degludec):

- 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

Although the insulin pen devices dial up in dose steps, for all the insulin products listed in the above table, the required dose (in units) is displayed in the dose counter window of the prefilled pen or cartridge and pen as a visual check of the dose to be administered.

For further information on reducing risk of medication error with Tresiba, see the April 2013 Drug Safety Update article[9] on Tresiba, the letter on Tresiba sent to healthcare professionals[10] and the Tresiba summary of product characteristics[11].

3.2. Key message:

Healthcare professionals and patients need to understand the dose conversion when switching between standard and high strength insulin products.

3.3. Switching between standard and high strength insulin products

There is **no need for dose conversion** when transferring patients from the standard to high strength version of the same insulin or vice versa for Humalog 100 units/ml and 200 units/ml and for Tresiba 100 units/ml and 200 units/ml.

However, although Toujeo (insulin glargine 300 units/ml) is a concentrated insulin glargine product, the manufacturer's Summary of Product Characteristics (SPC)[12] states that Toujeo and Lantus are not bioequivalent and **are not directly interchangeable.** The SPC advises:

- Switching from Lantus to Toujeo can be done unit-to-unit based on previous dose, but a higher Toujeo dose (approximately 10-18%) may be needed to achieve an equivalent clinical response.
- When switching from Toujeo to Lantus, the dose should be reduced by 20%.
- Close metabolic monitoring is required during any switch of insulin and in the initial weeks afterwards

The Toujeo guidance for healthcare professionals[13] highlights key safety elements when switching insulins.

Of particular note for Toujeo: although it is more concentrated than Lantus, the pen device will still only deliver a maximum of 80 units per injection, albeit in a lower injection volume. This is for safety reasons to ensure that large doses of the higher strength product are not given inadvertently if the wrong insulin is supplied or administered. However, due to the predicted dose increase required for those patients administering doses of Lantus above 65-70 units, a change to Toujeo could result in a requirement for administering two injections instead of one to achieve the same overall blood glucose lowering response. This could be a disadvantage when the main purpose of the higher strength insulins is to reduce the number of daily injections.

4. Biosimilar Insulins

A biosimilar medicine is a biological medicine that is similar to a medicine that has already been authorised to be marketed in the European Union (EU) (the biological reference medicine) with respect to quality, safety and efficacy.

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[14].

4.1. Key messages and practice points:

4.1.1. Brand name prescribing

Insulins should be prescribed by brand name to ensure that unintentional substitution of a biosimilar product does not occur when the medicine is dispensed.

4.1.2. Safety checks

Pharmacists should challenge any prescribing of insulin by its generic rather than brand name, to ensure that the product dispensed is the correct one intended for the

patient. Electronic prescribing systems should be reviewed to minimise the risk of prescribing the wrong product; this may include removal of the option of generic insulin glargine. Safety checks can be further supported by the use of the National Patient Safety Agency (NPSA) or a locally approved insulin passport

4.1.3. Switching between glargine products

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

5. Fixed combinations of insulin with other medicines

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 is a glucagon-like peptide-1 (GLP-1) receptor agonist.

Xultophy is administered as 'dose steps'. The dose counter on the pen shows the number of dose steps.

- One dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide.
- The maximum dose of Xultophy is 50 dose steps (50 units of insulin degludec and 1.8 mg of liraglutide).

Combination medicines can be advantageous to patients since they reduce the number of injections needed. However, there is a potential risk of patients receiving too little or too much of their medicine because of confusion that may arise over the way the doses are expressed for the individual components − the dose of the insulin is expressed in units while the dose of the non-insulin medicine is expressed in mg. Also, there is a reduction in flexibility of dosing as one drug dose cannot be altered without altering the dose of the second drug.

5.1. Key message:

Healthcare professionals and patients need to understand the insulin and GLP-1 strength of this (and future) products and how to use them correctly to minimise the risk of medication errors.

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[15].

Guidance for patients and healthcare professionals from the European Medicines Agency (EMA) Pharmacovigilance and Risk Assessment Committee (PRAC) Risk Minimisation strategy for high strength and fixed combination insulin products[16] is included in **Appendix 2.**

Appendix One: Abbreviations

Abbreviation	Definitions
MHRA	Medicines and Healthcare Product Regulatory
UKMi	UK Medicines Information Centre
SPC	Summary of Product Characteristics
EU	European Union
NPSA	National Patient Safety Agency
EMA	European Medicines Agency
PRAC	Pharmacovigilance and Risk Assessment Committee

Appendix Two: PRAC guidance on prevention of medication errors for patients, carers and healthcare professionals

High strength insulins

Recommendations for patients and carers:

- If the concentration of insulin stated on your medicine pack is **higher than 100 units/ml**, you are using a 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 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 a standard strength insulin you will usually be using the same number of units that you were when using the standard strength insulin. 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.
- Your healthcare professional will highlight any differences in design between your high-strength insulin device and other standard strength insulin devices, especially if you have been transferred **from a standard strength insulin to a high-strength insulin.**
- **You must never use a syringe to withdraw insulin from a pre-filled pen otherwise severe overdose may result.**
- During the switch to a 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 and their carers 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 a low-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 a 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 prefilled pen device for high-strength insulins and standard strength insulins, especially if the patient has been transferred from a standard strength insulin to a high-strength insulin. Focus on colour differentiation, warning statements on carton/label and other safety design features (such as tactile elements on the prefilled 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 the selection of any high-strength insulin.
    - Carefully check the product strength selected in electronic prescribing or dispensing systems.
- Ensure that storage arrangements for high-strength insulins facilitate correct selection of the medicine and avoid confusion with other medicines.

Combination Products

Recommendations for patients and carers

- Read the instructions in your package leaflet carefully before using your medicine.
- One dose step contains a set number of units of insulin plus a fixed amount of the non-insulin medicine. Before you use your medicine be clear on how many dose steps you require. Your healthcare professional will give you this information.

- Your healthcare professional will explain the design and features of your pen, including how the dose counter of the pen device shows the number of dose steps to be injected.
- During the switch to this type of combination medicine and in the weeks after the switch you should measure your blood sugar levels more frequently.
- If you have any questions about your treatment speak to your healthcare professional.

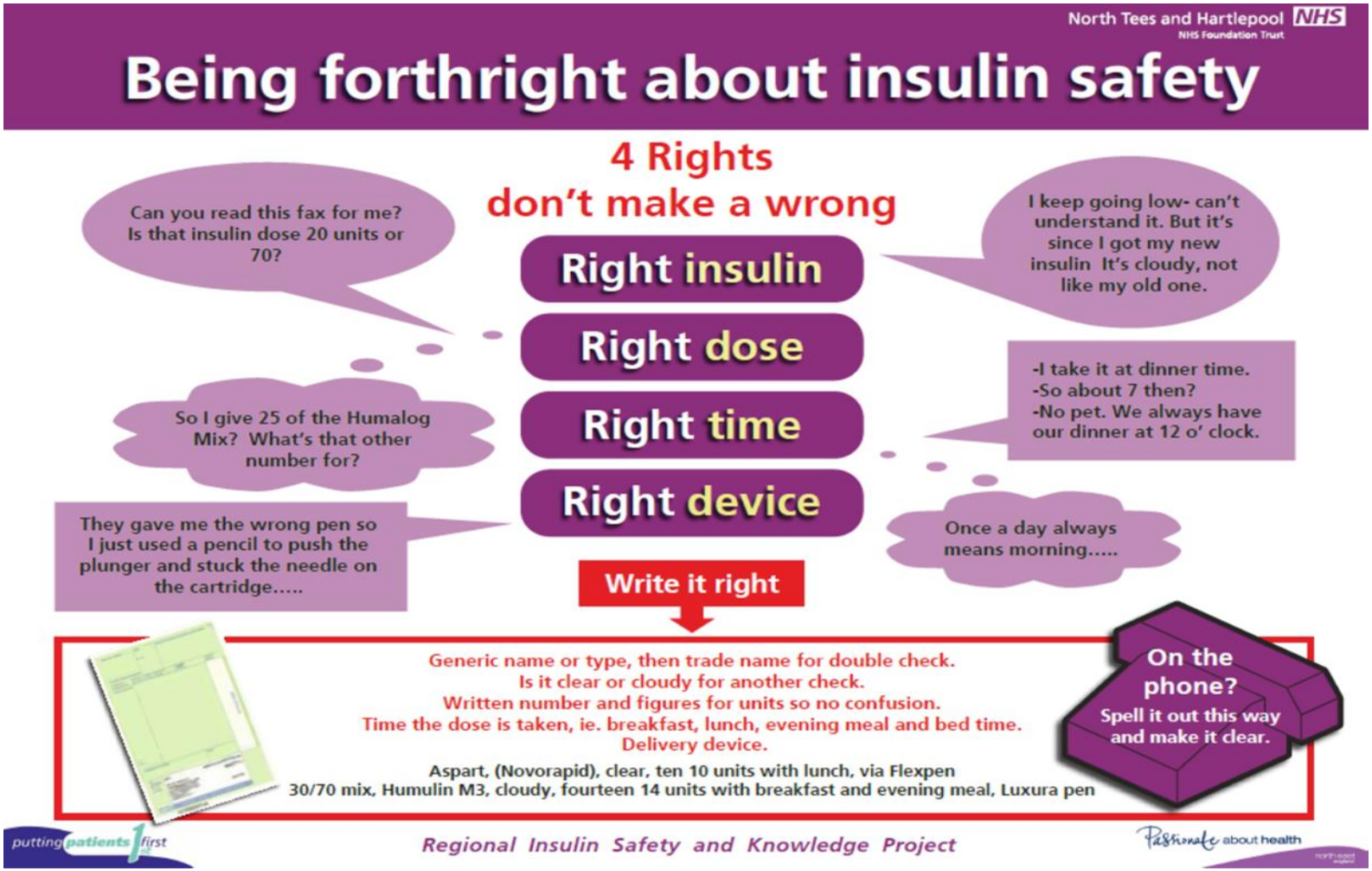
Recommendations for healthcare professionals

- Ensure that your patients and their carers are adequately informed on how to use their medicine.
- Explain to your patient that the dose counter of the pen device shows the number of dose steps to be injected. Always prescribe the dose of insulin and the dose of non-insulin to be injected as well as the dose frequency.
- If the patient has been transferred from another pen device, highlight the differences in design between the two devices.
- Pharmacists are encouraged to check that patients and carers are able to read 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.
- Tell patients to closely monitor their blood sugar levels when starting a medicine containing insulin and a non-insulin active substance and in the weeks after.

In addition, healthcare professionals are encouraged to take the following precautions when storing, prescribing and dispensing diabetes medicines that contain insulin in combination with a non-insulin active substance.

- Ensure that electronic and paper systems used to prescribe and dispense these medicines facilitate the selection of medicines containing insulin and a non-insulin active substance.
- 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.

Appendix Two: Insulin prescription safety poster



References

National Evidence Reviews

NICE have published the following Evidence Summary New Medicines reviews:

High strength insulin glargine 300 units/ml (Toujeo) in Type 1 diabetes – October 2015 (https://www.nice.org.uk/advice/esnm62/chapter/key-points-from-the-evidence)

Insulin glargine 100 units/ml biosimilar (Abasaglar) – December 2015 (https://www.nice.org.uk/advice/esnm64/chapter/key-points-from-the-evidence)

Further information

Toujeo guidance for patients and carers April 2015: https://assets.digital.cabinet-office.gov.uk/media/5537ad77ed915d15d8000017/Toujeo_guidelines_for_patients_2015.pdf

Letter on Humalog sent to healthcare professionals on 16 February 2015: https://assets.digital.cabinet-office.gov.uk/media/5537ac83e5274a1572000026/Humalog_DHPC_sent_16_Feb_2015.pdf

Drug Safety Update article on reducing risk of medication error with Tresiba: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266132

Adult insulin passport: http://www.nrls.npsa.nhs.uk/resources/?EntryId45=130397

Patient information booklet - Insulin, Use It Safely: http://www.nhsiq.nhs.uk/resource-search/publications/nhs-dakc-insulin-use-it-safely.aspx

Safe Use of Insulin e-learning NHS Improving Quality: http://www.nhsiq.nhs.uk/8473.aspx

Safer use of insulin CPPE learning module for pharmacists and pharmacy technicians: (https://www.cppe.ac.uk/programmes/l/insulin-p-01

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[1] the Medicines and Healthcare Product Regulatory (MHRA) : https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/424764/Drug_Safety_Update_-_April_2015.pdf,

[2] European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196980.pdf

[3] UKMi Safety Assessment Report for Toujeo and Abasaglar (insulin glargine) http://www.ukmi.nhs.uk/filestore/ukmiaps/InsulinglarginesOct-2015_1.pdf

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http://www.ukmi.nhs.uk/filestore/ukmiaps/InsulinglarginesOct-2015_1.pdf

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http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con228797.pdf

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[12] Manufacturer's Summary of Product Characteristics (SPC)
https://www.medicines.org.uk/emc/medicine/30586

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