IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR INSULIN GLARGINES

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND
Sanofi’s long-acting insulin glargine, 100 units/mL (Lantus®) solution for injection has been available since 2000. In 2015, Sanofi launched Toujeo®, a concentrated insulin glargine product of strength 300 units/mL. Toujeo® is available in the UK as two pre-filled pens: Toujeo® SoloStar® (1.5mL of solution equating to 450 units) and DoubleStar® (3mL solution equating to 900 units) which allows 160 units of insulin to be administered per single dose. Two biosimilar versions of insulin glargine (100 units/mL) are available in the UK: Abasaglar® (Eli Lilly) and more recently in 2019, Semglee® (Generics UK T/A Mylan).

The availability of five insulin glargine products (as multiple presentations) in the UK market creates a real potential for confusion in the prescribing, dispensing, and administration of these products. Lack of education on biosimilar products and lack of information on safety and differences in devices were identified as key barriers for the use of insulin biosimilars in primary care in a report produced for NHS England. This review summarises safety considerations associated with the use of high strength glargine products and the biosimilars. The RMOC position statement on ‘Insulin preparations: safety factors for local formulary decision-making (2018)’ has been considered as part of this review.

A UKMi briefing sheet: ‘Answers to commonly asked questions about biosimilar versions of insulin glargine (2015)’ is available Link

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL
The UKMi risk assessment (1) was applied to the insulin glargine products and compared with the originator glargine product, Lantus® (insulin glargine, 100 units/mL) solution for injection; Sanofi-Aventis (a formal assessment of Lantus® was not undertaken).

Assessments were carried out with reference to: images of the products; summaries of product characteristics (SmPC) and packaging inserts (2-10); Risk Minimisation Material (11-12); and the European Medicines Agency Reports for the products (13-14).

Overall the presentation, physical characteristics, and accompanying information of all products are considered appropriate. However, some inherent risks will be associated with the availability of five insulin glargine products. The main features and potential risks identified from the UKMi risk assessment (1) for the individual insulin glargine products are presented in Table 1 and summarised below. The images are presented in appendix 1.

- Overall the packaging and presentation between the insulin glargine products are well differentiated and should enable rather than hinder differentiation: the higher "300 units/mL" strength, for example, is highlighted in honey gold on the Toujeo® product packaging.
- It was noted that although the Toujeo SoloStar® and the Toujeo DoubleStar® are largely presented in different colours, the use of green in both products to some degree lessen the visual differentiation between them. Confusion between these two products is a particular risk as explained in the point below.
- Toujeo DoubleStar® is one of the very few insulin devices in the UK which administer 2 units of insulin per click. Therefore there is a risk patients could receive double the dose of insulin glargine if the wrong Toujeo product is dispensed or the Toujeo DoubleStar® is used incorrectly by assuming one click is
equivalent to one unit of insulin.

- Confusion between the other available insulin glargine products is possible. All presentations require refrigerated storage, which can restrict opportunities for physical separation, and hence particular risks may be present in pharmacy and other clinical locations where all products are kept together.
- Other points noted are that there is a small potential for sound and look alike name confusion between insulin glulisine and insulin glargine; tall man lettering (gIARGine) is used on the Abasaglar®, Semglee ™ and Toujeo® product packaging to aid differentiation.
- Glargine products are used across a range of care settings, and there are particular risks associated with this; for example, correct product selection at the transition between primary and secondary care. However, providing recommendations for full brand name prescribing (including the device name) for all insulin products are adhered to (15), the risk of confusion can be mitigated against.
- All known current clinical risks associated with Lantus® will apply equally to Abasaglar®, Semglee ™ and Toujeo®.
- Semglee ™ is subject to additional monitoring as indicated by the black triangle symbol for new medicines; the EMA Risk Management Plan (RMP) summarises safety concerns including: low blood sugar, immediate allergic reactions, reaction at injection site, malignancies, immunogenicity (13,14).
- Brand and batch specific safety surveillance for biosimilars is recommended (16); however given that insulins are predominantly prescribed and dispensed in primary care, in practice how can traceability for pharmacovigilance purposes be assured in this setting?

### POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

Potential next steps and mitigation actions can be considered in two respects: those of particular relevance to the NHS, and those of particular relevance to manufacturers.

Safe introduction of new insulin glargine products to the NHS will need to consider a number of actions:

1. **Brand name prescribing**
   - Insulin products should be prescribed by the brand name, followed by the concentration and recommended daily dose in units, and a statement of the presentation (i.e. cartridge or disposable pen); these actions are vital to identify products appropriately at the points of dispensing and/or administration. Particular care will be necessary at transition of care to ensure the correct product is selected. These safety checks can be further supported by the use of the NPSA or a locally approved insulin passport. As with all insulins, the product label must always be checked before each injection to avoid wrong product medication errors.
   - 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.
   - Education and training for prescribers, pharmacy staff, nurses, and others will also be necessary to inform healthcare professionals on the availability of all new insulin glargine products, differences in devices and to ensure brand name prescribing and identification occurs. Patient education to increase awareness of the product brand they are receiving will also be useful to reduce the potential for error.

2. **Switching between glargine products**
   As discussed in table 1 substitution and automatic switching from Lantus® to the biosimilars or between the biosimilars is not appropriate. Switching between insulin products has service workload implications and should only be carried out as part of a carefully planned programme by specialists. Such programmes will include: identification of suitable patient groups, dose switching protocols, and appropriate monitoring. Suitable patients
are likely to require full face-to-face assessment to allow shared decision-making and review in line with the local protocols.

3. **Storage**
Strategies to mitigate the risk of picking errors between the glargine products should be considered. These may include review of the stock’s location in pharmacies, in addition to rationalising which products are approved to be on the formulary and available locally.

4. **Device issues**
- Extreme care will be required to ensure patients and healthcare professionals are aware that the dose increments are in 2 units of insulin for the Toujeo DoubleStar® product. In general, all patients using insulin should be trained to check ‘the number of units’ dialled up on a pre-filled pen and not to rely on counting the number of clicks.
- For patients prescribed Toujeo® and Semglee ®, but subsequently unable to self-administer using the pre-filled pen (due to, for example, hospital admission), use of retractable pen needles will be required to reduce the risk of needle injury to healthcare staff.
- Care will be required to ensure the correct pen device is selected for the Abasaglar® cartridge formulation as the packaging and insert does not state the compatible pen device to be used. This may include rationalising the range of insulin cartridges kept within local organisations, with a view to minimising the number of pen devices held, and supporting correct pen selection.

5. **Reporting and monitoring of patients through pharmacovigilance**
Compliance with post-marketing surveillance systems is essential for safe introduction and on-going use. Access to brand name and batch number are necessary for clear traceability and identification. Currently Semglee ® is subject to additional monitoring.

In addition to actions for the NHS, this review previously (October 2015) highlighted one issue for, **Eli Lilly, the manufacturer of Abasaglar®**, which remains as of October 2019:

1. **Clarity on cartridge compatibility**
Information on the compatibility of the Abasaglar® cartridge with pen devices could be improved. Such information is presented on the dedicated website: [www.lillydiabetes.co.uk](http://www.lillydiabetes.co.uk), but clear information on the specific compatible pen could also be presented on the packaging and insert for the Abasaglar® cartridge product.

This updated review has also highlighted some issues for **Sanofi, the manufacturer of Toujeo®**:  
1. **Differentiation between the SoloStar® and DoubleStar® device**
Use of entirely different colours throughout the packaging and devices, including the dial, can further improve the visual differentiation between the products.
2. **Clarity on size of penfill**
Descriptions on pen size (1.5mL or 3mL) could be improved on product packaging by clearly specifying this on the front facing side of the outer packaging.
3. **Accessibility of risk minimisation material**
Risk minimisation material directed at patients are available on the Electronic Medicines Compendium [www.medicines.org.uk](http://www.medicines.org.uk), but could also be presented in the product packaging.
4. **Raise awareness of product availability**
Further promotion to raise awareness in both primary and secondary healthcare sectors of the key differences between the products.
Table 1: Summary of insulin glargine products available in the UK (2-10;17)

<table>
<thead>
<tr>
<th>Lantus® 100 units/mL (Sanofi)</th>
<th>Abasaglar® 100 units/mL (Eli Lilly)</th>
<th>Semglee® 100 units/mL (Generics UK T/A Mylan)</th>
<th>Toujeo SoloStar® 300 units/mL (Sanofi)</th>
<th>Toujeo DoubleStar® 300 units/mL (Sanofi)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Licensed indication</strong></td>
<td>Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.</td>
<td>Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.</td>
<td>Treatment of diabetes mellitus in adults.</td>
<td></td>
</tr>
<tr>
<td><strong>Product presentation</strong></td>
<td>Vial (5mL) Cartridge (3mL) Pre-filled pen (3mL)</td>
<td>Cartridge (3mL) Pre-filled KwikPen (3mL)</td>
<td>Pre-filled pen (3mL)</td>
<td>Pre-filled pen (1.5mL) Pre-filled pen (3mL)</td>
</tr>
<tr>
<td><strong>Suitable UK device for cartridge</strong></td>
<td>Allstar Pro Autopen 24 JuniorSTAR</td>
<td>HumaPen Luxura HD (stock only available till Sep 2020) HumaPen Savvio</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Maximum single dose (Pre-filled pen)</strong></td>
<td>1-80 units per single injection, in steps of 1 unit</td>
<td>1-80 units per single injection, in steps of 1 unit</td>
<td>1-80 units per single injection, in steps of 1 unit</td>
<td>2-160 units per single injection, in steps of 2 units (recommended for patients requiring at least 20 units per day)</td>
</tr>
<tr>
<td><strong>Interchangeability between insulin glargine products</strong></td>
<td>Substitution and automatic switching from Lantus® to the biosimilars cannot be undertaken, and would be counter to the MHRA’s recommendation that all biological medicines are prescribed by brand name. Similar principles will apply for interchangeability between the biosimilars.</td>
<td></td>
<td>Toujeo® (insulin glargine 300 units/mL) has a different formulation to Lantus®, Abasaglar®, Semglee® (insulin glargine 100 units/mL): it has been designed as a longer-acting product. Toujeo® (insulin glargine 300 units/mL) and Lantus®, Abasaglar®, Semglee® insulin glargine 100 units/mL are not bioequivalent and are not directly interchangeable. Direct substitution is not expected.</td>
<td></td>
</tr>
<tr>
<td><strong>Switching between insulin glargine products</strong></td>
<td>Switching from Lantus® to the biosimilars would require a managed approach with blood glucose monitoring, since dosage adjustment could theoretically be required. At the time of writing, specific guidance on the service or workload implications associated with such switching were not available. Early experience shows switching therapy is consultant-led and occurs in</td>
<td></td>
<td>When switching from insulin glargine 100 units/mL to Toujeo®, blood glucose monitoring and dose adjustment will be required. Switching protocols are included in the Toujeo® product literature When changing from Toujeo SoloStar® to Toujeo DoubleStar® the same dose can be used. But if the patient’s previous dose was an odd number (e.g. 23 units) then the dose must be increased or decreased by 1 unit (e.g. 24 or 22 units).</td>
<td></td>
</tr>
</tbody>
</table>
Secondary care or where consultants work closely with community teams. (18)

| Safety considerations | The packaging and insert for the Abasaglar® cartridge product specifies for a Lilly 3mL pen to be used but does not state the specific compatible pen device to be used. Confusion around this could potentially lead to use of incorrect selection of devices and improper delivery of the insulin dose. | Semglee® is only available as a pre-filled pen formulation and must be administered in this form, or severe overdose could result. Never use a syringe to remove Semglee®. | The Toujeo SoloStar® and the Toujeo DoubleStar® outer packaging includes descriptions such ‘1 step = 1 unit’ on the SoloStar® and ‘1 step = 2 units’ on the DoubleStar® packaging to highlight the difference between the products. Although the product packaging and devices are largely presented in different colours: green (Toujeo SoloStar®) or purple (Toujeo DoubleStar®), the use of green in both products lessen the visual differentiation between them. For example, the dial on both the SoloStar® and DoubleStar® devices are green. Considering the devices are fundamentally different: SoloStar® ‘1 step = 1 unit’ and DoubleStar® ‘1 step = 2 units’; use of entirely different colours throughout the packaging and devices would be more suitable. As with the other insulin glargine pre-filled preparations, the outer packaging does not clearly specify the size of the pen on the front facing side. However in this case as two sizes are available, 1.5mL or 3mL, this could add to the risk of confusion between the Toujeo products. The main concern with confusing the two products is that Toujeo DoubleStar® administers 2 units of insulin per click. There is a risk patients could receive double the dose of insulin glargine if the wrong Toujeo® product is prescribed/dispensed or the Toujeo DoubleStar® is used incorrectly by assuming one click is equivalent to one unit of insulin. Lack of familiarity/awareness on the availability of the two products (and the differences between them) by healthcare personnel compounds this issue. Both Toujeo® products are only available as pre-filled pen formulations and must be administered in this form, or severe

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overdose could result. A syringe should never be used to remove the glargine from the device.

<table>
<thead>
<tr>
<th>Links to Risk Management Material and</th>
<th>N/A</th>
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This report was produced in October 2019 using photographic images (not physical products) of products available at the time of assessment. Images were obtained primarily from pharmaceutical companies and from various sources within the NHS.

This report summarises product assessments undertaken by: London Medicines Information Service (Northwick Park Hospital) and London & South East Medicines Information Service (Guy’s Hospital). We are also grateful for the input of clinical specialists (diabetes) and the NHS Improvement Patient Safety Team in completing this piece of work. For comments email lnwh-tr.medinfo@nhs.net

The UKMi product safety assessment group would appreciate your views on the usefulness of this report. We have devised a short survey which we would appreciate you completing, it should take approximately 10 minutes to complete. Click the following link to complete the survey: https://www.surveymonkey.com/r/UKMiProductSafetyAssessments
References

8. Eli Lilly and Company Limited. Package leaflet: information for the user of Abasaglar 100 units/mL solution for injection in a pre-filled pen. Last revised July 2019.
10. Generics UK T/A Mylan. Package leaflet: information for the user of Semglee 100 units/mL solution for injection in a pre-filled pen. Last revised May 2018.
17. MIMS online. Insulin delivery devices. Available at www.mims.co.uk
APPENDIX 1: PRODUCT PHOTOS
ABASAGLAR®
KwikPen® 100 units/mL

solution for injection in a pre-filled pen
insulin glARGine

Subcutaneous use

Read the package leaflet before use.
Discard pen 28 days after first use.
5 pens of 3 mL.

EU/1/14/644/003

ABASAGLAR®
100 units/mL

solution for injection in a cartridge
Insulin glARGine

Subcutaneous use

These cartridges are for use with a Lilly 3 mL pen only.

Read the package leaflet before use.
Discard 28 days after first use.

5 cartridges of 3 mL.
Semglee® 100 units/ml
solution for injection in pre-filled pen
insulin glARGine
Subcutaneous use.

5 x pens of 3 ml

Mylan