# Drug Safety Update

## Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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## Contents



The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we inform you that the maximum adult daily dose of hydroxyzine has been reduced to 100 mg due to the risk of QT interval prolongation. Do not prescribe hydroxyzine to people with a prolonged QT interval or who have risk factors for QT interval prolongation—see article 1.

Codeine-containing medicines must not be used to treat symptoms of cough and cold in children under 12. Also, codeine is not recommended for adolescents (12 to 18) who have problems with breathing. This is due to the risk of respiratory side effects related to opiate toxicity—see article 2.

Several high strength, fixed combination and biosimilar insulin products have come to market recently. It is likely that further such insulin products will come to market over the next few years. This month, we summarise ways to minimise the risk of medication errors with these products. We encourage you to comment on the risk minimisation guidance for these products which is being developed by the European Medicines Agency. The consultation is open until 14th June 2015—see article 3.

Finally, in March 2015, letters were sent to healthcare professionals regarding ketoconazole HRA and radium-223 dichloride (Xofigo▼) —see article 4 for links to the letters.

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## 1 **Hydroxyzine (Atarax, Ucerax): risk of QT interval prolongation and Torsade de Pointes**

The maximum adult daily dose of hydroxyzine is now 100 mg. Do not prescribe hydroxyzine to people with a prolonged QT interval or risk factors for QT interval prolongation.

When using hydroxyzine:

- do not prescribe hydroxyzine to people with a prolonged QT interval or who have risk factors for QT interval prolongation (see below)
- avoid use in the elderly - they are more susceptible than younger patients to the side effects of hydroxyzine
- consider the risks of QT interval prolongation and Torsade de Pointes before prescribing to patients taking medicines that lower heart rate or potassium levels
- the maximum daily dose is now
    - 100 mg for adults
    - 50 mg for the elderly (if use cannot be avoided)
    - 2 mg per kg body weight for children up to 40 kg in weight
- prescribe the lowest effective dose for as short a time as possible
- continue to report any suspected side effects to hydroxyzine or any other medicine on a Yellow Card (www.mhra.gov.uk/yellowcard)

Hydroxyzine is an antihistamine used to treat pruritus in adults and children and anxiety in adults.

A European review of the safety and efficacy of hydroxyzine has been undertaken following concerns of heart rhythm abnormalities associated with this medicine. The review concluded that hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes. Such events are most likely to occur in patients who already have risk factors for QT prolongation, such as:

- concomitant use of medicines that prolong the QT interval
- cardiovascular disease
- family history of sudden cardiac death
- significant electrolyte imbalance (low potassium or magnesium levels)
- significant bradycardia

**Further information**

Letter sent to healthcare professionals in March 2015
https://assets.digital.cabinet-office.gov.uk/media/553faae3ed915d15d800002c/Hydroxyzine_DHPC_sent_31_March_2015.pdf

European Medicines Agency announcement March 2015
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyzine/human_referral_prac_000043.jsp&mid=WC0b01ac05805c516f

*Article citation: Drug Safety Update volume 8 issue 9 April 2015: 1*

## 2 **Codeine for cough and cold: restricted use in children**

Do not use codeine-containing medicines in children under 12 as it is associated with a risk of respiratory side effects related to opiate toxicity. Codeine is not recommended for adolescents (12 to 18) who have problems with breathing.

When prescribing or dispensing codeine-containing medicines for cough and cold, consider that:

- codeine is contraindicated in
    - children younger than 12 years old
    - patients of any age known to be CYP2D6 ultra-rapid metabolisers
    - breastfeeding mothers
- codeine is not recommended for adolescents (12 to 18) who have problems with breathing
- reporting suspected side effects to codeine or any other medicine on a Yellow Card (www.mhra.gov.uk/yellowcard) contributes to our understanding of medicine safety

Codeine is an opioid medicine that is authorised for pain relief and to treat the symptoms of cough and cold.

Codeine is converted into morphine by an enzyme called CYP2D6. Some people (known as ultra-rapid metabolisers) convert codeine into morphine faster than others. This results in high morphine levels in the blood, which can cause toxic effects such as breathing difficulties.

In 2010 the UK Commission on Human Medicines advised[1] that over-the-counter liquid medicines that contain codeine should not be used for cough suppression in people under 18.

**Review of codeine benefits and risks**

A European review has been conducted of the benefits and risks of using codeine to treat cough and cold symptoms in children. This followed the 2013 review of codeine for pain relief in children,[2] which was in response to some fatal and life-threatening cases of morphine intoxication.

The review concluded that there is limited evidence that codeine is effective for treating cough and cold symptoms in children. Although the impact of age on codeine metabolism is not fully understood, the current evidence suggests children under 12 are at a higher risk of serious side effects than children over 12. In addition, codeine can worsen symptoms in adolescents who already have problems with breathing.

We have received 26 Yellow Card reports of respiratory side-effects associated with the use of codeine in children up to 5 August 2014.

In line with recommendations for codeine when used for pain relief, codeine must not be taken by patients of any age known to be ultra-rapid metabolisers (see table in Drug Safety Update article from July 2013) or by breastfeeding mothers. Codeine can be passed through breast milk, which can harm the baby.

1. 'Codeine-containing liquid over-the-counter medicines' Drug Safety Update, October 2010 https://www.gov.uk/drug-safety-update/codeine-containing-liquid-over-the-counter-medicines

2. 'Codeine for analgesia: restricted use in children because of reports of morphine toxicity' Drug Safety Update, July 2013 https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity

**Further information**

European Medicines Agency announcement April 2015 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002316.jsp&mid=WC0b01ac058004d5c1

Drug Safety Update article on codeine for pain relief in children July 2013 https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity

*Article citation: Drug Safety Update volume 8 issue 9 April 2015: 2*

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## 3 **High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error**

Several new insulin products are now on the market. 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.

**Public consultation**

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 14th June 2015.

EMA consultation on the risk minimisation strategy for high strength and fixed combination insulin products, April 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<br>200 | FlexTouch prefilled pen |
| | Insulin lispro | Humalog | 100<br>200 | KwikPen prefilled pen |
| | Insulin glargine | Lantus | 100 | SoloSTAR prefilled pen |
| | | Toujeo▼ | 300 | |
| 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 units/mL cartridge | Lilly reusable pen |
| | | | 100 | KwikPen prefilled 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

Drug Safety Update article on Tresiba, April 2013 https://www.gov.uk/drug-safety-update/insulin-degludec-tresiba-available-in-additional-higher-strength
Letter on Tresiba sent to healthcare professionals Jan 2013 http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con228797.pdf
Tresiba summary of product characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf

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 guide for healthcare professionals.

Toujeo guidance for healthcare professionals April 2015 https://assets.digital.cabinet-office.gov.uk/media/5537acb140f0b61589000031/Toujeo_guidelines_for_healthcare_professionals_April_2015.pdf

**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.

Xultophy Summary of Product Characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002647/WC500177657.pdf

**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.

Abasaglar Summary of Product Characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002835/WC500175381.pdf

**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 https://assets.digital.cabinet-office.gov.uk/media/5537acb140f0b61589000031/Toujeo_guidelines_for_healthcare_professionals_April_2015.pdf
Toujeo guidance for patients and carers April 2015 https://assets.digital.cabinet-office.gov.uk/media/5537accae5274a1572000028/Toujeo_guidelines_for_patients_April_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 https://www.gov.uk/drug-safety-update/insulin-degludec-tresiba-available-in-additional-higher-strength
Letter on Tresiba sent to healthcare professionals in January 2013 http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con228797.pdf
Xultophy Summary of Product Characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002647/WC500177657.pdf
Abasaglar Summary of Product Characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002835/WC500175381.pdf
Adult insulin passport http://www.nrls.npsa.nhs.uk/resources/?EntryId45=130397
Patient information booklet http://www.nhsiq.nhs.uk/resource-search/publications/nhs-dakc-insulin-use-it-safely.aspx

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## 4 **Letters sent to healthcare professionals in March 2015**

In each issue of Drug Safety Update we summarise drug safety letters sent to healthcare professionals that are not linked to their own Drug Safety Update article. In March 2015, letters were sent regarding:

- Ketoconazole HRA: information about the risk of hepatotoxicity – sent by HRA Pharma on 24 March 2015
- Radium-223 dichloride (Xofigo▼): change in NIST Standard Reference Material – sent by Bayer on 19 March 2015

Ketoconazole HRA letter sent on 24 March 2015 https://assets.digital.cabinet-office.gov.uk/media/5537a3d740f0b6158900002f/Ketoconazole_DHPC_sent_24_March_2015.pdf

Radium-223 dichloride (Xofigo▼) letter sent on 19 March 2015 https://assets.digital.cabinet-office.gov.uk/media/5537a3f0e5274a1575000023/Xofigo_DHPC_sent_19_March_2015.pdf

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