Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the MHRA and its independent advisor the Commission on Human Medicines

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Contents

The **MHRA** 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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In this issue: the basal insulin analogue **insulin degludec** (Tresiba▼) is available in prefilled pen devices in two strengths: 100 units/mL; and 200 units/mL. The 100 units/mL strength is also available in a cartridge. All other approved basal insulins are available at 100 units/mL. Tresiba pen devices have dose-counter windows that show the number of units of insulin degludec that will be injected, irrespective of strength. Therefore no dose conversion is needed when transferring a patient from one strength of Tresiba to a different strength; however care is needed to ensure that the devices are used correctly (article A1).

Also this month: **cilostazol** (Pletal) is restricted to second-line treatment because of the potential risks of cardiovascular and bleeding events. Cilostazol is now contraindicated in patients with: unstable angina, or a recent myocardial infarction or coronary intervention (within 6 months), or any history of severe tachyarrhythmia. It is also contraindicated in patients receiving two or more other antiplatelet or anticoagulant treatments. See article A2 for further information.

And finally this month, we would like to remind healthcare professionals to remain vigilant with regard to drug names because serious errors have occurred when medicines with similar names have been confused. For example, mercaptopurine has been mistakenly prescribed instead of mercaptamine, which resulted in a life-threatening case of pancytopenia (see article H1).

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Drug safety advice

A1 Insulin degludec (Tresiba▼): available in additional higher strength than existing insulins—care needed to minimise risk of error, including training for patients

Insulin degludec (Tresiba▼) is available in prefilled pen devices (known as FlexTouch) in two strengths: 100 units/mL; and 200 units/mL. The 100 units/mL strength is also available in cartridge form (called Penfill). The 200 units/mL strength is higher than that of other existing basal insulin products in the UK. Ensure the correct insulin product and strength is prescribed and dispensed.

The dose-counter window of the Tresiba FlexTouch pen device shows the number of units that will be injected, irrespective of strength. Therefore no dose conversion is needed when transferring a patient from one strength of Tresiba to a different strength.

Patients should be trained on the correct use of Tresiba products, and always visually verify the dialled units on the dose counter of the prefilled pen device (irrespective of strength). Advise patients to seek medical advice immediately if they think they have administered an incorrect dose of Tresiba

Insulin degludec (Tresiba▼) has been developed as a once-daily basal insulin for the treatment of glycaemia in adult patients with diabetes mellitus. While administration at the same time of day is preferable, Tresiba allows for some flexibility in the timing of insulin injections. A minimum of 8 hours between injections should always be ensured.

Tresiba is available in pre-filled pen devices (called FlexTouch) in two strengths: 100 units/mL; and 200 units/mL. The 100 units/mL strength is also available in cartridge form (called Penfill, for use in specific insulin delivery systems). The prefilled pen devices have a dose-counter window that shows the number of units of insulin degludec that will be injected, irrespective of strength. Therefore no dose conversion is needed when transferring a patient from one strength of Tresiba to a different strength.

Patients should be trained on the correct use of the Tresiba products, in particular how to check the dose displayed on the prefilled pen device. Ensure that the strength is included on the prescription and dispensing label. Patients should be aware of the different strengths.

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

The pens and packaging of Tresiba are different for the two strengths. A letter on the safe use of Tresiba, including pictures of the different products, was sent to healthcare professionals in January 2013.

Advice for healthcare professionals:

Prescribing:

- When prescribing insulin degludec, ensure that the strength is included on the prescription
- Do not convert (ie, recalculate) doses when transferring patients from one strength of insulin degludec to another—the pen device shows the number of units of insulin to be injected irrespective of strength

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Dispensing:

- Pharmacists should ensure that the correct strength of insulin degludec is dispensed; if in doubt, contact the prescriber

- Pharmacists should ask patients to visually identify the strength of insulin degludec dispensed, and should ensure patients are able to read the dose counter of the pen device. Ask patients with poor vision to always seek assistance from a person who has good vision and is appropriately trained in use of the device

Administration:

- Patients and healthcare staff must never use a syringe to withdraw insulin from a prefilled pen or from a cartridge

Transfer from other medicines:

- Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted

- For most patients, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous basal insulin dose with subsequent individual dose adjustments

Information to give to patients:

- Patients should be aware that there are two different strengths of insulin degludec, and should be informed that the pen device will calculate the dose of insulin that they need irrespective of strength, so they simply need check the dose-counter window of the pen device which displays the dose in units, and make sure this matches the dose they wish to administer. Patients must never count audible clicks to determine the dose of Tresiba to be administered

- Patients should be provided with a patient booklet and Insulin Passport (or safety card), and should be trained on the correct use of Tresiba before the product is prescribed or dispensed

- Warn patients that they should only use Tresiba as they have been trained because using it any other way may result in a dangerous overdose

- Patients must be instructed to always check the manufacturer's packaging and dispensing label before every injection to ensure they have the correct Insulin

Clinical management and storage:

- Healthcare providers should risk assess electronic and paper systems used to prescribe, dispense and administer Tresiba. Carefully check the product strength selected in electronic systems

- Risk assess the clinical storage arrangements for Tresiba to help ensure selection of the correct strength

Further information

BNF section 6.1: Drugs used in diabetes:
http://www.medicinescomplete.com/mc/bnf/current/PHP4035-insulins.htm

NHS guidance on supporting safe treatment in diabetes:
http://www.diabetes.nhs.uk/safety/#

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A2 **Cilostazol (Pletal): risks of cardiovascular and bleeding events—indication restricted to second-line treatment and contraindicated with some cardiovascular conditions and medicines**

Cilostazol (Pletal) is restricted to second-line use in patients for whom life-style modifications and other appropriate interventions have failed to sufficiently improve their symptoms.

Furthermore, cilostazol is now contraindicated in patients with any of the following:

- unstable angina, recent myocardial infarction or coronary intervention (within 6 months)
- a history of severe tachyarrhythmia
- those receiving two or more other antiplatelet or anticoagulant treatments

For patients starting cilostazol, prescribers should assess benefit after 3 months of treatment, and should stop treatment if patients have not made clinically relevant improvements in walking distance. All patients who are currently receiving long-term treatment should be reassessed at a routine appointment, in light of the new advice

Cilostazol (Pletal) is a phosphodiesterase type 3 inhibitor indicated for the improvement of walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis (Fontaine stage II). The effects of cilostazol include antiplatelet activity and vasodilation.

A review of the benefits and risks of cilostazol was triggered by reports of adverse reactions (mainly cardiac and haemorrhagic), and by the potential for drug interactions.

Efficacy of cilostazol

In clinical trials, cilostazol provided an average improvement in maximum walking distance of 87 m (approximately 66% increase) compared with 44 m for placebo; average baseline walking distance was 133 m. The studies measured walking distance using a graded treadmill test, and therefore the actual improvement on flat ground is expected to be greater.

Safety review of cilostazol

CASTLE trial: http://www.sciencedirect.com/science/article/pii/S0741521407016096

Safety data from the efficacy trials and a phase IV long-term safety study (CASTLE) were reviewed. The most commonly reported reactions were relatively minor (headaches, diarrhoea, palpitations, dizziness), and the clinical trials did not raise serious safety concerns. However cilostazol has been shown to increase heart rate by about 5–7 beats per minute, and this may put some patients at increased risk of cardiac events (eg, those with stable coronary disease). Contraindications have been revised to exclude patients at greatest risk of cardiac adverse events.

The CASTLE trial had a primary endpoint of all-cause mortality and included more than 1400 patients. Although the trial was terminated early due to a low event rate and high drop-out, it was considered to provide some reassurance on cardiovascular safety. No increase in bleeding risk was found with cilostazol alone or combined with one other antiplatelet treatment (clopidogrel or aspirin). However, there was a higher frequency of bleeding events when cilostazol was combined with both clopidogrel and aspirin.

Cilostazol is mainly metabolised via CYP3A4 and CYP2C19. Exposure to cilostazol is increased if it is taken concomitantly with medicines that inhibit these enzymes. Pharmacokinetic data from interaction studies has been reviewed and a dose reduction (to 50 mg twice a day) is now recommended when cilostazol is taken with strong inhibitors of these enzymes. The increase in overall pharmacological activity when cilostazol is taken with ketoconazole or erythromycin is around 35%; when taken with

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omeprazole it is increased by about 47%.

Conclusions of the review

The benefit provided by cilostazol is clinically relevant in some patients and the risks associated with treatment in these patients are manageable. However, in patients with some cardiovascular conditions or those receiving two or more other antiplatelet or anticoagulant treatments, the risks of cilostazol outweigh the benefits.

Advice for healthcare professionals:

- Cilostazol is restricted to second-line treatment where lifestyle modifications (eg, smoking cessation and exercise regimens) and other appropriate interventions have failed to provide sufficient improvement. Lifestyle changes should continue during treatment
- Cilostazol is contraindicated in patients with:
  - unstable angina, recent myocardial infarction or coronary intervention (within 6 months)
  - history of severe tachyarrhythmia
  - those receiving two or more other antiplatelet or anticoagulant treatments
- Advise patients to take cilostazol 30 minutes before breakfast and evening meal
- Reassess patients after 3 months of starting cilostazol and consider stopping treatment if there is no clinically relevant improvement in walking distance
- A dose reduction to 50 mg twice a day is recommended when cilostazol is taken in combination with any of the following: erythromycin; clarithromycin; ketoconazole; itraconazole; omeprazole; or any strong inhibitors of CYP3A4 or CYP2C19
- Reassess patients currently receiving long-term treatment with cilostazol at a routine appointment, in order to advise on treatment continuation, dose change, or cessation

Further information

EMA press release and link to agreed product information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/03/news_detail_001746.jsp&mid=WC0b01ac058004d5c1

BNF section 2.6.4: Peripheral vasodilators and related drugs: http://www.medicinescomplete.com/mc/bnf/current/PHP1396-cilostazol.htm

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Bulletin continues…

Hot topic

H1 **Recent drug-name confusion: please be vigilant as life-threatening errors may occur**

We have recently been made aware of medication errors resulting from patients being prescribed or supplied with the wrong medicine from the list below, due to confusion between similarly named products.

Take particular care when prescribing or dispensing these medicines because their names could be confused with each other (ie, they sound alike or look alike).

Recent examples of medicine names that have been confused resulting in medication errors include:

- Mercaptamine and mercaptopurine
- Sulfadiazine and sulfasalazine
- Risperidone and ropinirole
- Zuclopenthixol decanoate and zuclopenthixol acetate

See Drug Safety Update, October 2010: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096800

Some of these errors could result in life-threatening conditions. We previously issued a reminder to remain vigilant when prescribing mercaptamine or mercaptopurine after a case of a 9-month-old who was erroneously prescribed mercaptopurine instead of mercaptamine by their GP. After approximately 1 month of incorrect treatment, the child was admitted to hospital with pancytopenia; the child fortunately made a full recovery.

Remember that the medicines listed above are used to treat different conditions or patients:

Mercaptamine is indicated for the treatment of proven nephropathic cystinosis
Mercaptopurine is indicated for the treatment of acute leukaemia

Sulfadiazine is indicated for the prevention of rheumatic fever
Sulfasalazine is used in the treatment of: mild to moderate and severe ulcerative colitis and maintenance of remission; active Crohn's disease; and rheumatoid arthritis

Risperidone is used in schizophrenia and other psychoses
Ropinirole is used in Parkinsonism and related disorders

Zuclopenthixol acetate is used in schizophrenia and other psychoses
Zuclopenthixol decanoate is used in long-acting formulations for patients with schizophrenia in whom oral maintenance therapy is unreliable

If pharmacists have any doubt about which of these medicines is intended they should contact the prescriber before dispensing the drug. Health professionals should remain vigilant when dealing with these medicine names, which either look alike when written or sound alike. In addition, ensure that the correct medicine name is chosen from any drop-down lists in a prescribing database.

Yellow Card: www.mhra.gov.uk/yellowcard

Please report any suspected adverse drug reactions, including those arising from medication errors, to the MHRA through the Yellow Card Scheme.

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Stop press

S1 **Strontium ranelate (Protelos): risk of serious cardiac disorders—restricted indications, new contraindications, and warnings**

A review of available safety data for strontium ranelate (Protelos) has raised concern about its cardiovascular safety beyond the already recognised risk of venous thromboembolism. An analysis of randomised controlled trial data has identified an increased risk of serious cardiac disorders, including myocardial infarction (relative risk compared with placebo was 1.6 [95% CI 1.07–2.38]).

The European Medicines Agency will fully evaluate the benefits and risks of strontium ranelate in the coming months. In the meantime, in order to help minimise these risks, updated advice is available:

Advice for healthcare professionals:

- Use of strontium ranelate is now restricted to treatment of severe osteoporosis
  - in postmenopausal women at high risk of fracture
  - in men at increased risk of fracture
- Treatment should only be initiated by a physician with experience in the treatment of osteoporosis, and the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks
- Strontium ranelate should not be used in patients with: ischaemic heart disease, peripheral arterial disease; cerebrovascular disease; a history of these conditions; or in patients with uncontrolled hypertension
- Prescribers are advised to assess the patient's risk of developing cardiovascular disease before starting treatment and thereafter at regular intervals
- Patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or if hypertension is uncontrolled
- Healthcare professionals should review patients at a routine appointment and consider whether or not to continue treatment

Further information

European Medicines Agency updated information on strontium ranelate: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001774.jsp&mid=WC0b01ac058004d5c1

Suspected adverse reactions to strontium ranelate should be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard).

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Medicines and Healthcare Products Regulatory Agency