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

Volume 12 Issue 3 October 2018

Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency 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.

NICE accredited
www.nice.org.uk/accreditation

MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

To subscribe to monthly email alerts of Drug Safety Update see: https://www.gov.uk/drug-safety-update

First, following negative interim results of a clinical trial in an off-label use, rivaroxaban treatment in patients who have undergone transcatheter aortic valve replacement (TAVR) should be stopped and switched to standard of care (page 2). Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients.

Second, be aware of an interaction between the HIV medicine ritonavir and levothyroxine, used for replacement therapy in hypothyroidism (page 4). Post-marketing cases have been received of reduced thyroxine concentrations and increased thyroid-stimulating hormone (TSH) plasma concentration, including some cases leading to hypothyroidism, in patients concomitantly taking ritonavir-containing products and levothyroxine. TSH levels should be monitored for a month after the start of ritonavir treatment and a month after discontinuation.

Next, read about reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving ponatinib (Iclusig▼), indicated for certain leukaemias (page 5).

On page 7, we remind all healthcare professionals who prescribe and dispense fentanyl patches to ensure patients and their caregivers are aware of the potentially fatal consequences of accidental transfer of patches, particularly to a child, and have ready access to instructions for proper administration, use, and disposal of patches.

Finally, see the article on page 9 for a reminder of the supply disruption alert issued on management of the supply disruption of EpiPen and EpiPen Junior, including MHRA advice on extension of use beyond the expiry date for certain batches of EpiPen 300 microgram adrenaline autoinjectors.

drugsafetyupdate@mhra.gov.uk

Rivaroxaban (Xarelto▼) after transcatheter aortic valve replacement: increase in all-cause mortality, thromboembolic and bleeding events in a clinical trial

Rivaroxaban treatment in patients who undergo transcatheter aortic valve replacement (TAVR) should be stopped and switched to standard of care.

Advice for healthcare professionals:

- preliminary analysis of a phase 3 clinical trial show risks of all-cause death and bleeding post-TAVR were approximately doubled in patients assigned to a rivaroxaban-based anticoagulation strategy compared with those assigned to receive an antiplatelet-based strategy (clopidogrel and aspirin)
- rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients
- rivaroxaban treatment in patients who undergo TAVR should be stopped and switched to standard of care
- the direct-acting oral anticoagulants apixaban and edoxaban have not been studied in patients with prosthetic heart valves and their use is also not recommended in these patients; the use of dabigatran is contraindicated in patients with prosthetic heart valves requiring anticoagulant treatment
- report any suspected adverse drug reactions to rivaroxaban on a Yellow Card

GALILEO study design and findings

Study 17938 (GALILEO) is a randomised, open label, active-controlled, multicentre, phase 3 trial that aimed to assess clinical outcomes after successful TAVR in patients randomly assigned to receive either a rivaroxaban-based anticoagulation strategy or an antiplatelet-based strategy.

The first group was assigned to receive rivaroxaban 10 mg once a day and acetylsalicylic acid (aspirin) 75–100 mg once a day for 90 days followed by maintenance with rivaroxaban 10 mg once a day. The comparator group was assigned to receive clopidogrel 75 mg and acetylsalicylic acid 75–100 mg once a day for 90 days, followed by acetylsalicylic acid alone.

The primary efficacy endpoint is a composite of all-cause death, stroke, systemic embolism, myocardial infarction, pulmonary embolism, deep vein thrombosis, and symptomatic valve thrombosis. The primary safety endpoint is a composite of life-threatening or disabling (BARC types 5 and 3b/3c) and major (BARC type 3a) bleeding events. Patients with atrial fibrillation at randomisation were excluded.

The trial was stopped in August 2018, on recommendation of the independent Data Safety Monitoring Board (DSMB), following a preliminary analysis of available data. The trial findings suggested an imbalance between the two study groups in all-cause mortality, thromboembolic, and bleeding events (see table).

These results are preliminary and based on incomplete data collection. The final study data will be assessed by regulatory authorities as soon as they are available, including an assessment of any implications for approved indications. We will promptly communicate any relevant updates.

Event	Rivaroxaban group (n=826)	Antiplatelet group (n=818)
Death or first thromboembolic events	117 (11%)	87 (9%)
All-cause death	56 (7%)	27 (3%)
Primary bleeding events	36 (4%)	21 (2%)

Table: Preliminary findings of Study 17938

Data are number of events (% patients).

Background

Xarelto▼ (rivaroxaban) is a direct inhibitor of coagulation factor Xa with the following indications:

- Co-administered with acetylsalicylic acid alone or with acetylsalicylic acid plus clopidogrel or ticlopidine, for prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (2.5 mg)
- Co-administered with acetylsalicylic acid, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (2.5 mg)
- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (10 mg)
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (15 mg and 20 mg)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (10 mg, 15 mg, and 20 mg).

Rivaroxaban is not approved for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients.

Report any suspected adverse drug reactions

Xarelto▼ (rivaroxaban) is a black triangle drug. Please continue to report any suspected adverse drug reactions associated with rivaroxaban to the MHRA through the Yellow Card Scheme.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, product brand name, and batch number.

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 1.

Ritonavir-containing products: reports of interaction with levothyroxine leading to reduced thyroxine levels

Monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month after starting and ending ritonavir treatment.

Advice for healthcare professionals:

- reduced thyroxine levels have been reported in patients concomitantly taking ritonavir-containing products and levothyroxine
- monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month after the start and end of ritonavir treatment
- report suspected adverse drug reactions resulting from interactions on a Yellow Card

Review of interaction between ritonavir and levothyroxine

Pharmacovigilance Risk Assessment Committee recommendations on signals. Adopted at the 5-8 February 2018 PRAC meeting.

An EU review has assessed evidence for an interaction between ritonavir and levothyroxine following a signal of reduced thyroxine concentrations and increased TSH plasma concentrations in patients concomitantly taking these medicines. Some of the cases reported were symptomatic, including cases of hypothyroidism.

This interaction has been added to the Summaries of Product Characteristics and Patient Information Leaflets for ritonavir-containing medicines and levothyroxine.

Levothyroxine has a narrow therapeutic index and if ritonavir is stopped, any previous modifications to levothyroxine dose may have significant consequences for thyroxine levels. Induction of metabolism (glucuronidation) of levothyroxine by ritonavir is a possible mechanism for this interaction.

Monitor TSH during ritonavir changes

TSH should be monitored in patients receiving concomitant treatment with ritonavir and levothyroxine for at least the first month after starting and ending ritonavir treatment. The duration of the monitoring proposed is based on the pharmacokinetics of the drug—the half-life of thyroxine being 6–7 days.

Report drug interactions and access the latest safety information on the Yellow Card app

MHRA encourages the reporting of any suspected side effects, especially from interactions with medicines, food, or complimentary remedies such as herbals medicines. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

Your report helps the MHRA to monitor the safety of medicines in the UK and identify potential side effects and adverse reactions. By reporting a Yellow Card, you can prevent future harms to other patients – see our Yellow Card patient leaflet for more. Personal details are kept safe, secure, and confidential.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

You can also use the app to access the latest safety information from MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

About ritonavir and levothyroxine

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older). Ritonavir is also indicated for the treatment of chronic hepatitis C as part of a fixed-dose combination of ritonavir/ombitasvir/paritaprevir. The potential for an interaction with levothyroxine is already known for antivirals used in chronic hepatitis C treatment because paritaprevir and ombitasvir are inhibitors of uridine diphosphoglucuronate-glucuronosyltransferase 1A1.

Levothyroxine is indicated for the control of hypothyroidism.

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 2.

Ponatinib (Iclusig▼): reports of posterior reversible encephalopathy syndrome

Interrupt treatment if posterior reversible encephalopathy syndrome (PRES) is confirmed and resume treatment only once the event is resolved and the benefit of continued treatment outweighs the risk of PRES.

Advice for healthcare professionals:

- post-marketing cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving ponatinib; the risk could be up to 1 in 100 people taking the medicine
- presenting signs and symptoms of PRES include seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances
- interrupt treatment if PRES is confirmed and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of PRES
- advise patients to contact their healthcare professional immediately if they develop sudden-onset severe headache, confusion, seizures, or vision changes
- black triangle medicines are intensively monitored to ensure that any new safety hazards are identified promptly – report any suspected adverse drug reactions on a Yellow Card

Reports of posterior reversible encephalopathy syndrome

A routine EU review assessed cases of posterior reversible encephalopathy syndrome reported in patients receiving ponatinib. In a cumulative review, 5 cases of PRES were identified, 2 of which were confirmed with MRI. Two cases showed a positive de-challenge effect (symptoms improved after ponatinib withdrawal). In both cases, signs and symptoms of PRES did not reappear when ponatinib was restarted at a lower dose (negative re-challenge at reduced dose).

Risk of PRES has been added to the list of adverse events associated with ponatinib in the Summary of Product Characteristics and Patient Information Leaflet with a frequency of uncommon (could affect up to 1 in 100 people taking the medicine).

No UK Yellow Card reports have been received for PRES association with ponatinib treatment, but use in the UK is low and continued vigilance is recommended.

About posterior reversible encephalopathy syndrome (PRES)

PRES is a neurological disorder that can present with signs and symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances.[1] Characteristic radiographic findings include bilateral regions of subcortical vasogenic oedema that resolve within days or weeks.

Hypertension including hypertensive crisis is an established reaction associated with ponatinib treatment and may contribute to the risk of PRES.

1. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015; 14: 914–25.

About ponatinib (Iclusig▼)

Iclusig is indicated for adult patients with:

- Chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Prescribers are reminded of previous advice on dose reduction in relation to the risk of serious vascular occlusive events with this medicine (see Drug Safety Update, April 2017).

.

Report any suspected adverse drug reactions

Please continue to report any suspected adverse reactions to Ponatinib via the Yellow Card Scheme. Your report will help us safeguard public health.

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 3.

Transdermal fentanyl patches: life-threatening and fatal opioid toxicity from accidental exposure, particularly in children

Provide clear information to patients and caregivers about how to minimise the risk of accidental exposure and the importance of appropriate disposal of patches. We continue to receive reports of unintentional opioid toxicity and overdose of fentanyl due to accidental exposure to patches.

Advice for healthcare professionals:

- always fully inform patients and their caregivers about directions for safe use for fentanyl patches, including the importance of:
  - not exceeding the prescribed dose
  - following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application
  - not cutting patches and avoiding exposure of patches to heat including via hot water (bath, shower)
  - ensuring that old patches are removed before applying a new one
  - following instructions for safe storage and properly disposing of used patches or those which are not needed (see instructions below)
- ensure that patients and caregivers are aware of the signs and symptoms of fentanyl overdose (see below) and advise them to seek medical attention immediately (by dialing 999 and requesting an ambulance) if overdose is suspected
- in patients who experience serious adverse events, remove patches immediately and monitor for up to 24 hours after patch removal
- report any cases of accidental exposure where harm has occurred or suspected side effects via the Yellow Card Scheme

Background

Accidental exposure to transdermal fentanyl can occur if a patch is swallowed or transferred to another individual (see Drug Safety Update, September 2008, and Drug Safety Update, July 2014). In 2014, following an EU review, advice on minimising risk of accidental transfer added to Summary of Product Characteristics and the Patient Information Leaflet for transdermal fentanyl products.

Reports of accidental exposure to transdermal fentanyl

We continue to receive reports of preventable accidental transfer of fentanyl patches. Since July 2014 and up to October 2018, we have received 5 reports of fatal incidents specifying accidental exposure, accidental overdose, or product adhesion issue. Causes of death was not included in all reports but were understood to be related to opioid toxicity.

Provide clear information to patients and caregivers

All healthcare professionals, particularly those involved in the prescribing and dispensing of fentanyl patches, should provide clear information to patients and caregivers regarding risk of accidental transfer and ingestion of patches, and need for appropriate disposal of patches.

Advise patients and caregivers to follow closely the instructions on the patch packaging, the carton, and in the accompanying Patient Information Leaflet. To help you discuss this with patients, we have produced an updated patient and caregiver information sheet (large print version).

Urgent medical attention should be sought for anyone accidentally exposed to a fentanyl patches. Administration of naloxone may help to reverse an opioid overdose.

Storage and disposal of fentanyl patches

Fentanyl patches should be stored out of sight and reach of children. After use, patches should be folded so that the adhesive side of the patch adheres to itself and then placed back into the original sachet. Used patches should be kept out of sight and reach of children – even used patches contain some medicine that may harm children and may even be fatal.

Patients are advised to talk to their pharmacist about safe disposal of patches, both used and unused.

Signs and symptoms of fentanyl overdose

Warn patients and caregivers of possible symptoms of fentanyl overdose, which include respiratory depression (difficulty in breathing or shallow breathing); tiredness; extreme sleepiness or sedation; inability to think, walk, or talk normally; and feeling faint, dizzy, or confused. Opioid overdose can be fatal and requires urgent medical treatment.

About fentanyl

Fentanyl is a potent opioid analgesic—a 25 µg per hour fentanyl patch equates to daily doses of oral morphine of up to 90 mg. Fentanyl patches should be used only in patients who have previously tolerated opioids because of a risk of significant respiratory depression in opioid-naive patients.

The initial dose of fentanyl should be based on a patient's opioid history. Please consult the summaries of product characteristics (SPC) for information on starting doses and dose conversion.

Report harm from accidental exposure to the Yellow Card Scheme

Please report medication errors resulting in harm, including accidental exposure to a medicine, or suspected side effects on a Yellow Card.

Your report helps to improve the safety of medicines in the UK. Never assume someone else will report an adverse drug reaction – if in doubt, report via the Yellow Card website or Yellow Card App (download via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices).

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 4.

Letters and drug alerts sent to healthcare professionals in September 2018

All healthcare professionals should be aware of the recent supply disruption alert from the Department of Health & Social Care (DHSC) on management of the supply disruption of EpiPen and EpiPen Junior. MHRA has allowed an extension of use beyond the expiry date for certain batches of EpiPen 300 microgram adrenaline autoinjectors.

Patients can continue to use the EpiPen 300 microgram auto-injectors of specified lots safely until the extended use-by date in the table. Further information about batches affected can be found within the alert and on the EpiPen website.

In September 2018, MHRA issued the following Alerts and recalls for drugs:

- Class 4 defect information: Olmetec 20mg Film Coated Tablets (MDR 12-08/18). 3 September 2018. Error on the blister foil of specific batches of Olmetec 20mg Film-Coated Tablets

- Company-led recall: Mydriasert 0.28mg/5.4mg Ophthalmic Insert. 11 September 2018. Thea Pharmaceuticals are recalling a specific batch of Mydriasert 0.28mg/5.4mg Ophthalmic Insert as it is labelled as being for the French market, rather than the UK market

- Class 4 defect information: Caspofungin 70mg powder for concentrate for solution for infusion (MDR 11-09/18). 18 September 2018. Error on the patient information leaflet for Caspofungin 70mg powder for concentrate for solution for infusion

- Company-led Drug Alert: Imatinib 400mg Capsules (3 x 10) PL 36390/0180. 21 September 2018. Error on the Patient Information Leaflet (PIL): the dosage information for the indication CML is incorrect

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 5.

Medical Device Alerts issued in September 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

The following alerts were recently issued:

- Flex connectors in Halyard Closed Suction Kits – risk of interruption of ventilation (MDA/2018/030). 19 September 2018 – Manufactured by Halyard Health. Risk of some flex connectors in closed suction kits becoming loose or disconnecting, which may interrupt patient ventilation.

- SureSigns VS & VM patient monitors and Viewing stations manufactured before May 2018: risk of batteries overheating or igniting (MDA/2018/031). 19 September 2018 – Manufactured by Philips. Lithium ion batteries which have exceeded their specified replacement interval or number of charging cycles are at risk of overheating or igniting.

- Various trauma guide wires – risk of infection due to packaging failure (MDA/2018/032). 24 September 2018 – Manufactured by Zimmer Biomet with expiry dates prior to 31 May 2028. Wire may breach packaging, compromising sterility of device.

Article citation: Drug Safety Update volume 12, issue 3: October 2018: 6.