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 July 2012, we advised that the contraindications for dabigatran had been clarified to include a range of clinical conditions where the patient is at significant risk of major bleeding, as well as in combination with other anticoagulant agents (see http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON175429). Because similar risks are associated with the other new oral anticoagulants apixaban and rivaroxaban, these contraindications have been applied across all three new oral anticoagulants for all indications and doses. See article A1 for further advice.

Also this month, read our Yellow Card Scheme update about how information on reporting suspected side effects to medicines will be appearing in Patient Information Leaflets for the first time (article Y1).

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Drug safety advice

A1 New oral anticoagulants apixaban (Eliquis▼), dabigatran (Pradaxa) and rivaroxaban (Xarelto▼): risk of serious haemorrhage—clarified contraindications apply to all three medicines

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON175429

We previously advised that the contraindications for dabigatran had been clarified to include a range of clinical conditions where the patient is at significant risk of major bleeding, as well as in combination with other anticoagulant agents. Because similar risks are associated with the other new oral anticoagulants (apixaban and rivaroxaban), these contraindications have been applied across all three new oral anticoagulants for all indications and doses

Dabigatran (Pradaxa) is a potent, orally active, direct inhibitor of free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Apixaban (Eliquis ▼) and rivaroxaban (Xarelto ▼) are direct, highly selective, orally active inhibitors of activated factor X (factor Xa).

All three new oral anticoagulants are licensed for:

- prevention of venous thromboembolic events in adults who have had elective total hip-replacement or knee-replacement surgery
- prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors

Rivaroxaban is additionally licensed for:

- treatment of deep-vein thrombosis and pulmonary embolism, and prevention of their recurrence, in adults

Risk of haemorrhage

[redacted]

oral anticoagulants have some differing contraindications due to their different properties, the contraindications in patients with conditions putting them at significant risk of major bleeding, and those relating to use with other concomitant anticoagulants, now apply to all three of the medicines. This is the result of a European review.

Updated advice on contraindications and warnings:

The following contraindications now apply to all three new oral anticoagulants, for all doses and indications:

- A lesion or condition, if considered a significant risk factor for major bleeding. This may include:
  - current or recent gastrointestinal ulceration
  - presence of malignant neoplasm at high risk of bleeding
  - recent brain or spinal injury
  - recent brain, spinal, or ophthalmic surgery
  - recent intracranial haemorrhage
  - known or suspected oesophageal varices
  - arteriovenous malformation
  - vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent—eg, unfractionated heparin, low molecular weight heparin (such as enoxaparin or dalteparin), heparin derivatives (such as fondaparinux), or oral anticoagulants (such as warfarin).

Continues…

Exceptions are switching of therapy to or from the medicine, or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter

Additional advice and information for healthcare professionals:

- Special care should be taken when deciding to prescribe these anticoagulant medicines to patients with other conditions, procedures, and concomitant treatments (eg, non-steroidal anti-inflammatory drugs, antiplatelets), which may increase the risk of major bleeding

- Attention should be paid to renal function. Impaired renal function may constitute a contraindication or recommendation not to use the anticoagulant medicine, or may require a dose reduction; recommendations differ for the three medicines

- The contraindications, posology, and warnings and precautions for use specific to each medicine, together with the individual's risk factors for bleeding (eg, renal function), should be considered before prescribing these medicines

There is no specific antidote available for any of these three new oral anticoagulants. Please consult the product information for advice on treatment in the event of bleeding complications, or overdose.

A full list of contraindications, warnings and information on posology can be found in the individual Summaries of Product Characteristics for apixaban, dabigatran, and rivaroxaban.

Summaries of Product Characteristics:

Apixaban: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002148/human_med_001449.jsp&mid=WC0b01ac058001d124],

Dabigatran: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124

Rivaroxaban http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&mid=WC0b01ac058001d124

Further information

Letter for healthcare professionals sent Sept 29, 2013: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON321824

Drug Safety Update articles July 2012 (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON175429) and December 2011 (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771)

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Yellow Card Scheme update

See also Drug Safety Update May 2013: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON282740

Further information

European Medicines Agency announcement , Oct 1 2013: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/09/news_detail_001900.jsp&mid=WC0b01ac058004d5c1

Yellow Card Scheme helps protect public health: www.mhra.gov.uk/yellowcardcasestudies and www.mhra.gov.uk/yellowcardimpact

Y1 **Black triangle symbol (▼) in Patient Information Leaflets**

For the first time, patients and the public will start to see information in Patient Information Leaflets about how to report suspected side effects via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

The Yellow Card Scheme is a vital early-warning system, collecting information from healthcare professionals and the wider public to help monitor the safety of medicines. It helps us take action to make changes to the warnings for a medicine, or review the way a medicine is used to maximise benefit and minimise risk.

In the UK, the black triangle (▼) has been in place for many years to aid the monitoring of new medicines through encouraging the reporting of suspected adverse reactions; it has now been adopted for use in Europe. A list of black triangle medicines can be found at: www.mhra.gov.uk/blacktriangle.

For the first time, patients will start to see the black triangle (▼) in the Patient Information Leaflet for relevant medicines. The leaflet will explain that the medicine is subject to additional monitoring to allow quick identification of new safety information, and that patients can help by reporting any side effects.

Patients, parents, or carers may ask you questions about the black triangle (▼) symbol or reporting of side effects. Please encourage these enquirers to report any suspected side effects via the Yellow Card Scheme, reiterating the guidance in the Patient Information Leaflet about potential side effects of the medicine (and what to do). It may be important to explain that: the symbol means that the medicine is being monitored particularly closely; this is generally because there is less information available about it compared with other medicines (eg, because it is new to the market or there is limited data on its long-term use); and that the symbol does not mean the medicine is unsafe.

Do not worry about duplicate reports if a Yellow Card is submitted by both a professional and a patient (or carer) for the same suspected adverse reaction. We are able to detect duplicate reports and use the combined information provided when assessing each case.

Remember that guidelines remain the same for healthcare professionals: any suspected adverse drug reaction can be reported on a Yellow Card. We are particularly interested in hearing about all those that are associated with black triangle (▼) medicines.

How to report

For healthcare professionals and the wider public alike, it is easiest and quickest to report online at www.mhra.gov.uk/yellowcard. If you choose to register, you can also keep track of any Yellow Cards that you send.

You can also get Yellow Card forms by:

- emailing yellowcard@mhra.gsi.gov.uk
- downloading them from the Yellow Card website www.mhra.gov.uk/yellowcard

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Medicines and Healthcare Products Regulatory Agency