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Questions and answers on the review of bleeding risk with Pradaxa (dabigatran etexilate)

On 24 May 2012, the European Medicines Agency completed a review of the risk of bleeding with the anticoagulant medicine Pradaxa, in order to assess whether the latest available data show any higher risk than previously recognised. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the data on Pradaxa are consistent with the well-known risk of bleeding with anticoagulant medicines and that there is no change in the risk profile of the medicine, but decided that further information should be added to the product information to clarify the guidance for prescribers and patients on how to reduce and manage this risk.

What is Pradaxa?

Pradaxa is an anticoagulant (a medicine that prevents the blood from clotting). It can be used in adults to prevent blood clots forming in the veins following knee or hip replacement surgery, or to prevent strokes and blood clots in patients with an abnormal heart beat called non-valvular atrial fibrillation. The active substance in Pradaxa, dabigatran etexilate, is converted in the body into dabigatran, which works by blocking the action of a substance called thrombin, which is central to the process of blood clotting.

Pradaxa was first authorised in the EU in March 2008 for its use following surgery. It was approved for use in patients with non-valvular atrial fibrillation in the EU in August 2011. Pradaxa is marketed in all EU Member States as well as Norway, Iceland and Liechtenstein. The current European public assessment report for Pradaxa can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

What issue was assessed with Pradaxa?

The risk of bleeding with anticoagulant medicines is well known and was reflected in the prescribing information for Pradaxa at the time of initial authorisation. This risk has been kept under close review by the CHMP, which has monitored the number of serious bleedings reported with Pradaxa since its authorisation, including fatal cases. In January 2012, further precautions were included in the prescribing information following reports of fatal cases of bleeding which occurred in Japan. The updates focused on patients with reduced kidney function, as dabigatran is eliminated by the kidneys

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

and a reduced function can lead to an increased amount of dabigatran in the bloodstream, increasing the risk of bleeding. In January 2012 the CHMP decided that an in-depth assessment of the latest available data was appropriate to determine if the risks were any greater than understood at the time of authorisation, and if the prescribing information could be further strengthened to increase the safety of patients.

Which data has the CHMP reviewed?

The CHMP considered the available data on the risk of serious or fatal bleeding with Pradaxa, gathered since its authorisation from clinical trials and post-marketing surveillance.

What are the conclusions of the CHMP?

The CHMP concluded that the latest available data are consistent with the known risk of bleeding and that the risk profile of Pradaxa was unchanged. The Committee found that frequency of reported fatal bleedings with Pradaxa was significantly lower than what had been observed in clinical trials at the time of authorisation, but considered that the risks should nonetheless continue to be kept under close review.

The Committee considered that the product information for Pradaxa already contains appropriate measures to prevent and manage this risk of bleeding, but decided that certain recommendations for prescribers and patients should be clarified and strengthened by adding further information. For prescribers, this includes details on the specific situations where Pradaxa must not be used, identifying the types of lesions or conditions and the concomitant medications which put patients at significant risk of major bleeding. It also includes details on how kidney function should be assessed and on options for managing patients and reversing the anticoagulant effect of Pradaxa if bleeding occurs.

In addition, the CHMP noted that reports of bleeding with Pradaxa often involved the patient having an accident or injury. Therefore the CHMP decided that advice should be included in the package leaflet for patients to seek urgent medical attention if they fall or injure themselves during treatment.

The full changes made to the information to doctors and patients are detailed here.

What is the updated advice for patients taking Pradaxa?

- Patients should seek urgent medical attention if they fall or injure themselves during treatment, especially if they hit their head, due to the increased risk of bleeding.
- Patients taking other anticoagulants (medicines to prevent blood clotting) must not take Pradaxa except during a period where their treatment is being switched to or from Pradaxa.
- Patients who have any questions should speak to their doctor or pharmacist.

What is the updated advice for prescribers?

- Prescribers are reminded of the need to follow all the necessary precautions with regard to the risk of bleeding with Pradaxa, including the assessment of kidney function before treatment in all patients and during treatment if a deterioration is suspected, as well as dose reductions in certain patients.
- Pradaxa must not be used in patients with a lesion or condition putting them at significant risk of major bleeding (see the revised product information for details).

- Pradaxa must not be used in patients using any other anticoagulant, unless the patient is being switched to or from Pradaxa (see the revised product information for details).

A European Commission decision on this opinion will be issued in due course.