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No change is needed in use of direct oral anticoagulants following EMA-funded study

No change to the conditions of use of the direct oral anticoagulants Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) is needed following a review of the results of a European study of real-world data for these medicines.

The study, commissioned by EMA and using real-world data from Denmark, France, Germany, Spain, the Netherlands and the United Kingdom, assessed the risk of serious bleeding with these 3 medicines when used to prevent blood clotting in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart) and compared this with other oral anticoagulants called vitamin K antagonists.[1,2]

The results were reviewed by EMA's human medicines committee (CHMP), in consultation with EMA's safety committee (PRAC), and were compared with data from other similar studies and in the published literature.

EMA's review concluded that the pattern of serious bleeding seen in patients taking Eliquis, Pradaxa and Xarelto was similar to that seen in the clinical trials on which the authorisation of the medicines were based. The data were not sufficient to allow robust conclusions to be drawn on comparisons between the 3 medicines.

The study also looked at whether the use of the medicines in clinical practice was in line with the authorised uses and took into account existing contraindications, warnings and advice on interactions with other medicines. EMA concluded that no changes to the product information were warranted, as the data did not provide robust evidence of a high level of non-adherence to the authorised product information.

The study results provided further data on the known increased risk of bleeding in older patients (>75 years). The companies marketing these direct oral anticoagulant medicines will be asked to further explore the issue and to investigate whether changes to the recommended doses could be beneficial for these patients.

[1] EU PAS register no. 16014: http://www.encepp.eu/encepp/viewResource.htm?id=28664
[2] Ibáñez, L et al. British Journal of Clinical Pharmacology. Nov 2019 85: 2524. Incidence of direct oral anticoagulant use in patients with nonvalvular atrial fibrillation and characteristics of users in 6 European countries (2008–2015): A cross-national drug utilization study https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.14071 . Two further publications in preparation.

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Information for patients

- A study was carried out on the use of the anticoagulant medicines Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban). These medicines prevent blood clots in a number of situations, including in patients with non-valvular atrial fibrillation. Blood clots can cause serious problems when they occur in important organs such as the lungs and brain. However, because these medicines prevent clotting, bleeding in various parts of the body can be an unwanted side effect.
- The study looked at bleeding in patients with non-valvular atrial fibrillation (irregular rapid contractions of the heart) treated with one of the 3 medicines and compared with other anticoagulant medicines such as warfarin.
- EMA has reviewed the results of the study and concluded that the risk of bleeding with the medicines was as expected. The study did not show that there was a high level of incorrect use of the medicines.
- EMA recommends that Eliquis, Pradaxa and Xarelto can continue to be used in the same way as they are now by patients and healthcare professionals and there is no need to change the current advice for these medicines.
- Based on the study results, which show that older patients (>75 years) are at greater risk of bleeding, EMA will ask the companies marketing these medicines to explore the issue and investigate whether changes to the dosing recommendations for older patients could be beneficial for these patients.
- If you have any questions about your medicines, talk to your doctor or pharmacist.

Information for healthcare professionals

- A retrospective, non-interventional study using European databases was carried out in 6 countries to assess the risk of major bleeding associated with use of direct oral anticoagulants (DOACs) when compared to vitamin K antagonists (VKAs), in patients with non-valvular atrial fibrillation. The study had been proposed following a workshop held by EMA in 2015[3] on the clinical use of DOACs.
- Overall, the new data confirm the bleeding patterns of DOACs versus VKA already observed in clinical trials and described in the product information of the medicines. The benefit-risk balance remains positive for all three DOACs investigated (apixaban, dabigatran, rivaroxaban) within the authorised indications. Comparable results were found in similar studies conducted in Canada and the US.
- The study also looked at adherence with sections 4.1, 4.3, 4.4, and 4.5 of the summary of product characteristics for the medicines. EMA concluded that the data did not provide robust evidence of a high level of non-adherence to the authorised product information.
- There was an observation of increased risk of bleeding in older patients (>75 years). Further studies are needed to explore the issue and to determine whether there are differences in risk between individual DOACs. The data were not sufficient to recommend dosage changes in this population. The companies marketing these medicines will be asked to explore the issue and to

3 https://www.ema.europa.eu/en/events/role-pharmacokinetic-pharmacodynamic-measurements-use-direct-oral-anticoagulants-doacs

carry out an analysis to determine whether modification of the dosing recommendations could be beneficial for older patients.

More about the medicine

The direct oral anticoagulants Eliquis (apixaban), Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban) are taken by mouth to prevent blood clotting in a number of situations, including in patients with non-valvular atrial fibrillation. They are also used to treat deep vein thrombosis (a blood clot in a deep vein, usually in the leg) and pulmonary embolism (a clot in a blood vessel supplying the lungs), and to prevent these conditions from reoccurring.

These medicines work by directly blocking a single blood clotting factor in the body; this is why they are called 'direct anticoagulants' as opposed to other anticoagulants such as warfarin that indirectly target various clotting factors.

More information about these medicines can be found on the EMA website:

www.ema.europa.eu/medicines/human/EPAR/pradaxa
www.ema.europa.eu/medicines/human/EPAR/eliquis
www.ema.europa.eu/medicines/human/EPAR/xarelto

More about the procedure

The review of direct oral anticoagulants was initiated on 31 January 2019 at the request of the EMA Executive Director, under Article 5(3) of Regulation 726/2004.

The review has been carried out by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's opinion.