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EPAR summary for the public

Xarelto

rivaroxaban

This is a summary of the European public assessment report (EPAR) for Xarelto. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Xarelto.

What is Xarelto?

Xarelto is a medicine that contains the active substance rivaroxaban. It is available as tablets (2.5, 10, 15 and 20 mg).

What is Xarelto used for?

Xarelto is used for the following in adults:

- to prevent venous thromboembolism (VTE, the formation of blood clots in the veins) in patients who are undergoing surgery to replace a hip or knee;
- to prevent stroke caused by a blood clot in the brain and systemic embolism (a blood clot in a blood vessel) in patients with non-valvular atrial fibrillation (irregular rapid contractions of the upper chambers of the heart);
- to treat deep vein thrombosis (DVT, 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 DVT and pulmonary embolism from re-occuring.
- to prevent atherothrombotic events (problems caused by blood clots and hardening of the arteries) after an acute coronary syndrome. Acute coronary syndrome is a group of conditions that includes unstable angina (a severe type of chest pain) and heart attack. It is used together with antiplatelet medicines, which prevent the blood from clotting.

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The medicine can only be obtained with a prescription.

How is Xarelto used?

When Xarelto is used to prevent venous thromboembolism in patients undergoing hip or knee replacement surgery, the recommended dose is 10 mg once daily. Treatment with Xarelto should start six to 10 hours after surgery, provided that the patient is no longer bleeding from the site of surgery. Treatment should continue for five weeks in patients who have had hip replacement surgery, and for two weeks in patients who have had knee replacement surgery. The tablets can be taken with or without food.

When Xarelto is used to prevent stroke or systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 20 mg once daily. Treatment with Xarelto should be continued provided the benefit outweighs the risk of bleeding. The tablets are taken with food.

When Xarelto is used to to treat DVT and pulmonary embolism or to prevent DVT and pulmonary embolism from re-occuring, the recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily. The tablets are taken with food.

When Xarelto is used to prevent atherothrombotic events in patients who have had acute coronary syndrome, the recommended dose is 2.5 mg taken twice a day. It should be taken either in combination with aspirin or together with aspirin and clopidogrel or aspirin and ticlopidine. Treatment should start as soon as possible after the acute coronary syndrome has stabilised. The benefits of ongoing treatment should be regularly evaluated by your doctor against the risk of bleeding.

In patients with reduced kidney function the dose of Xarelto may need to be adjusted.

How does Xarelto work?

Patients undergoing hip or knee replacement surgery and patients with atrial fibrillation, DVT, pulmonary embolism or who have had acute coronary syndrome are at a risk of blood clots forming or re-occuring and moving to another part of the body. The active substance in Xarelto, rivaroxaban, is a ‘factor Xa inhibitor’. This means that it blocks factor Xa, an enzyme that is involved in the production of thrombin. Thrombin is central to the process of blood clotting. By blocking factor Xa, the levels of thrombin decrease, which reduces the risk of blood clots forming in the veins and arteries, and also treats existing clots.

How has Xarelto been studied?

For the prevention of VTE after surgery, Xarelto was compared with enoxaparin (another medicine that prevents the blood from clotting) in three main studies, two in patients undergoing hip replacement surgery and one in patients undergoing knee replacement surgery. In hip replacement surgery, the first study compared five weeks of Xarelto with five weeks of enoxaparin in around 4,500 patients, and the second study compared five weeks of Xarelto with two weeks of enoxaparin in around 2,500 patients. The third study compared two weeks of Xarelto with two weeks of enoxaparin in around 2,500 patients undergoing knee replacement surgery. In all of the studies, the effectiveness was measured by looking at the number of patients who either had blood clots in the veins or in the lungs, or who died of any cause during the treatment period.

For the prevention of stroke and systemic embolism, Xarelto was compared with warfarin (another medicine that prevents the blood from clotting) in one main study in 14,264 patients with non-valvular atrial fibrillation. The main measure of effectiveness was the number of patients who had either a stroke or a blood clot in a blood vessel.

For DVT and pulmonary embolism, Xarelto was compared with enoxaparin given in combination with a vitamin K antagonist, VKA, in two main studies in 3,449 patients with acute DVT and 4,833 patients with pulmonary embolism, respectively. The main measure of effectiveness was the number of patients who had either a DVT recurrence or pulmonary embolism.

For the prevention of atherothrombotic events in patients who have had acute coronary syndrome, Xarelto was compared with placebo (a dummy treatment) in one main study involving over 15,000 patients who had recently had an acute coronary syndrome. All patients also received standard antiplatelet medicines. The main measure of effectiveness was the number of patients who had an 'event' such as a heart attack or stroke or who died due to heart problems during the study.

What benefit has Xarelto shown during the studies?

In the three studies in patients undergoing surgery, Xarelto was more effective than enoxaparin in preventing the formation of blood clots or death. In the first study in hip replacement surgery, 1% of the patients who completed treatment with Xarelto either had blood clots or died (18 out of 1,595), compared with 4% of the patients receiving enoxaparin (58 out of 1,558). In the second study, 2% of the patients taking Xarelto had blood clots or died (17 out of 864), compared with 9% of the patients receiving enoxaparin (81 out of 869). After knee replacement surgery, 10% of the patients receiving Xarelto had blood clots or died (79 out of 824), compared with 19% of the patients receiving enoxaparin (166 out of 878).

In the study in patients with non-valvular atrial fibrillation, 2.7% (188 out of 6958) of patients treated with Xarelto had either a stroke or a blood clot in a blood vessel, compared with 3.4% (241 out of 7004) of patients receiving warfarin.

In the study in patients with acute DVT, 2.1% (36 out of 1,731) of patients treated with Xarelto had either DVT recurrence or pulmonary embolism, compared with 3.0% (51 out of 1,718) of patients receiving enoxaparin/VKA. In the study in patients with pulmonary embolism, 2.1% (50 out of 2,419) of patients treated with Xarelto had a recurrence of either DVT or pulmonary embolism, compared with 1.8% (44 out of 2,413) of patients receiving enoxaparin/VKA.

In the study in patients who have had acute coronary syndrome, 6.1% (313 out of 5,114) of patients treated with Xarelto had an 'event' such as a heart attack, stroke or death due to heart problems during the study, compared with 7.4% (376 out of 5,113) of patients receiving placebo.

What is the risk associated with Xarelto?

The most common side effects with Xarelto (seen in between 1 and 10 patients in 100) are anaemia, dizziness, headache, bleeding in various parts of the body, hypotension (low blood pressure), haematoma (collection of blood under the skin), pain in the stomach and belly, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, ecchymosis (bruising), pain in the extremities, decreased kidney function, fever, peripheral oedema (swelling, especially of the ankles and feet), decreased general strength and energy, increased levels of some liver enzymes in the blood and oozing of blood or fluid from the surgical wound in patients undergoing surgery.

For the full list of all side effects reported with Xarelto, see the package leaflet.

Xarelto must not be used in people who are hypersensitive (allergic) to rivaroxaban or any of the other ingredients. It must not be used in patients who are bleeding or in patients who have a liver disease or a condition that is associated with an increased risk of bleeding. Xarelto must not be used together with any other medicines called anticoagulants that prevent the blood from clotting, except in specific

conditions. Xarelto must not be used in women who are pregnant or breast-feeding. For the full list of restrictions, see the package leaflet.

Why has Xarelto been approved?

The CHMP decided that Xarelto's benefits are greater than its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe use of Xarelto?

The company that markets Xarelto will provide an educational pack for doctors expected to prescribe Xarelto for patients with atrial fibrillation, DVT, pulmonary embolism, or who have had acute coronary syndrome, containing important safety information including on the risk of bleeding during treatment with Xarelto and how to manage this risk. Prescribers will also receive a patient alert card to give to patients receiving Xarelto containing key safety reminders for patients.

The company will also carry out a large study to gather more data on the safety of Xarelto when used in patients who have had acute coronary syndrome.

Other information about Xarelto

The European Commission granted a marketing authorisation valid throughout the European Union for Xarelto on 30 September 2008.

The full EPAR for Xarelto can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports. For more information about treatment with Xarelto, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 05-2013.