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Xarelto (*rivaroxaban*)

An overview of Xarelto and why it is authorised in the EU

What is Xarelto and what is it used for?

Xarelto is an anticoagulant medicine (a medicine that prevents blood clotting) used:

- 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 reccuring in adults;
- to prevent venous thromboembolism (VTE, the formation of blood clots in the veins) in adults who are undergoing surgery to replace a hip or knee;
- to treat VTE and prevent VTE from recurring in children and adolescents aged less than 18 years;
- to prevent stroke (caused by a blood clot in the brain) and systemic embolism (a blood clot in another organ) in adults with non-valvular atrial fibrillation (irregular rapid contractions of the upper chambers of the heart);
- to prevent atherothrombotic events (such as heart attack, stroke or death from heart disease) in adults:
  - after an acute coronary syndrome, when it is used with an antiplatelet medicine (which prevents the formation of blood clots). Acute coronary syndrome consists of conditions such as unstable angina (a severe type of chest pain) and heart attack;
  - at high risk of ischaemic events (problems caused by restricted blood supply) who have coronary artery disease (disease caused by obstructed blood supply to the heart muscle) or peripheral artery disease (disease caused by defective blood flow in the arteries). It is used with aspirin.

Xarelto contains the active substance rivaroxaban.

How is Xarelto used?

Xarelto is available as tablets and granules for making an oral suspension. The dose and duration of treatment with Xarelto depend on what it is being used for and the patient's risk of bleeding. For children, the form, dose and duration of treatment also depend on the patient's age and weight.

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Xarelto is given at a lower dose (2.5 mg twice daily) when used in combination with an antiplatelet medicine such as aspirin, clopidogrel or ticlopidine. The doctor will regularly evaluate the benefits of ongoing treatment against the risk of excessive or internal bleeding.

The medicine can only be obtained with a prescription. For more information about using Xarelto, see the package leaflet or contact your doctor or pharmacist.

How does Xarelto work?

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.

What benefits of Xarelto have been shown in studies?

Treatment and prevention of DVT and pulmonary embolism

For DVT and pulmonary embolism, Xarelto was compared with enoxaparin (another anticoagulant medicine) given in combination with a vitamin K antagonist, VKA (a class of anticoagulants such as warfarin), in two main studies in around 3,400 adults with acute DVT and in around 4,800 with pulmonary embolism. In the study in patients with acute DVT, 2.1% (36 out of 1,731) of patients treated with Xarelto had either another DVT or pulmonary embolism, compared with 3.0% (51 out of 1,718) of patients receiving enoxaparin and VKA. In the study in patients with pulmonary embolism, 2.1% (50 out of 2,419) of patients treated with Xarelto had either DVT or pulmonary embolism again, compared with 1.8% (44 out of 2,413) of patients receiving enoxaparin and VKA.

An additional study involved over 3,000 adults who had completed 6 to 12 months of treatment for DVT and pulmonary embolism. Patients received either 10 mg or 20 mg Xarelto daily, or aspirin daily for an additional 12 months. Results showed that 1.5% of patients in the Xarelto 20 mg group, 1.2% of patients in the Xarelto 10 mg group and 4.4% of patients in the aspirin group had DVT or pulmonary embolism again or died.

Prevention of VTE after surgery

For the prevention of VTE after surgery, Xarelto was more effective than enoxaparin in three main studies, two in adults undergoing hip replacement surgery and one in adults undergoing knee replacement surgery:

- The first study found that 1% of the patients undergoing hip replacement surgery and who completed 5 weeks of treatment with Xarelto had blood clots or died (18 out of 1,595), compared with 4% of the patients receiving enoxaparin (58 out of 1,558).
- The second study found that 2% of the patients taking Xarelto for 5 weeks for hip replacement surgery had blood clots or died (17 out of 864), compared with 9% of the patients receiving enoxaparin (81 out of 869) for 2 weeks.
- The third study found that 10% of the patients receiving Xarelto for 2 weeks had blood clots or died (79 out of 824), compared with 19% of the patients receiving enoxaparin (166 out of 878) for 2 weeks.

Prevention of stroke and systemic embolism

For the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, Xarelto was more effective than warfarin in one main study in over 14,000 adult patients: 2.7% (188 out of 6958) of patients taking Xarelto had a stroke or a blood clot, compared with 3.4% (241 out of 7004) of patients taking warfarin.

Prevention of atherothrombotic events

For the prevention of atherothrombotic events in patients with acute coronary syndrome, Xarelto was compared with placebo (a dummy treatment) in one main study involving over 15,000 adults who had recently had an acute coronary syndrome. All patients also received standard antiplatelet medicines. In the study in patients who have had acute coronary syndrome, 6.1% (313 out of 5,114) of patients treated with Xarelto had a heart attack, stroke or died due to heart problems during the study, compared with 7.4% (376 out of 5,113) of patients receiving placebo.

In a study involving around 30,000 patients at high risk of ischaemic events with coronary artery disease or symptomatic peripheral artery disease, 4.1% (379 out of 9,152) of patients treated with Xarelto and aspirin had a heart attack, stroke or died due to heart problems during the study, compared with 5.4% (496 out of 9,126) of patients receiving aspirin and placebo.

Treatment of VTE and prevention of VTE recurrence in children

Xarelto was compared with standard-of-care anticoagulation medicines in the prevention of VTE recurrence in children and adolescents aged less than 18 years old with acute VTE. In a study involving 500 patients, 1.2% (4 out of 335) of patients treated with Xarelto had recurrent VTE, compared with 3% (5 out of 165) of those treated with either a heparin medicine or a vitamin K antagonist.

What are the risks associated with Xarelto?

The most common side effects with Xarelto (which may affect up to 1 in 10 people) are bruising and bleeding in various parts of the body, anaemia, dizziness, headache, hypotension (low blood pressure), pain in the stomach and belly, dyspepsia (indigestion), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, pain in the arms and legs, 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 a surgical wound.

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

Xarelto must not be used in patients who are bleeding or in patients who have a liver disease or a condition that increases the risk of bleeding. Xarelto must not be used together with any other anticoagulant medicines, except in specific circumstances. Xarelto must not be used in women who are pregnant or breast-feeding. For the full list of restrictions, see the package leaflet.

Why is Xarelto authorised in the EU?

The European Medicines Agency decided that Xarelto's benefits are greater than its risks and it can be authorised for use in the EU.

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

The company that markets Xarelto will provide an educational pack for doctors who prescribe Xarelto, containing important safety information including on the risk of bleeding during treatment with Xarelto and how to manage this risk. In addition, it will provide a patient alert card containing key safety reminders for patients receiving Xarelto.

The company will also provide a training video to explain to healthcare professionals and caregivers how to properly prepare and give the Xarelto oral suspension.

The company will also gather more data on the safety of Xarelto when used in patients who have had acute coronary syndrome.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Xarelto have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Xarelto are continuously monitored. Side effects reported with Xarelto are carefully evaluated and any necessary action taken to protect patients.

Other information about Xarelto

Xarelto received a marketing authorisation valid throughout the EU on 30 September 2008.

Further information on Xarelto can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/xarelto.

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