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EPAR summary for the public

Pradaxa

dabigatran etexilate

This is a summary of the European public assessment report (EPAR) for Pradaxa. 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 Pradaxa.

What is Pradaxa?

Pradaxa is a medicine that contains the active substance dabigatran etexilate. It is available as capsules (75, 110 and 150 mg).

What is Pradaxa used for?

Pradaxa is used for the following:

- to prevent the formation of blood clots in the veins in adults who have had an operation to replace a hip or knee;
- to prevent stroke and the formation of clots in adults who have an abnormal heart beat called 'non-valvular atrial fibrillation' and are considered to be at risk of stroke;
- to treat deep vein thrombosis (DVT, a blood clot in a deep vein, usually in the leg) and pulmonary embolism (PE, a clot in a blood vessel supplying the lungs), and to prevent these conditions from reoccurring in adults.

The medicine can only be obtained with a prescription.

How is Pradaxa used?

The capsules should be swallowed whole with water. For patients who have had a hip or knee replacement, treatment with Pradaxa should start with one 110 mg capsule taken one to four hours

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after the end of the operation. Treatment then continues with 220 mg (as two 110 mg capsules) once a day for 28 to 35 days after hip replacement and for 10 days after knee replacement.

The start of the treatment should be delayed in patients who are still bleeding from the site of surgery. If treatment is not started on the day of the operation, it should start at 220 mg (as two 110 mg capsules) once a day. A lower dose is used in patients with moderately reduced kidney function, in patients over 75 years of age, and in patients also taking amiodarone, quinidine or verapamil (medicines used to treat heart problems).

For the prevention of stroke and blood clots in patients with non-valvular atrial fibrillation, Pradaxa is taken as one 150 mg capsule twice a day and should be taken long term.

For the treatment and prevention of DVT and PE, Pradaxa is taken as one 150 mg capsule twice a day, following treatment for at least five days with an injectable anticoagulant .

For both the prevention of stroke and blood clots in patients with non-valvular atrial fibrillation, and for treatment and prevention of DVT/PE, a lower dose should be used in patients aged 80 or above, and in patients also taking verapamil.

All patients considered to be at increased risk of bleeding should be monitored closely and the dose of Pradaxa lowered at the discretion of the doctor.

In all patients, kidney function should also be assessed before starting treatment to exclude patients with severely reduced kidney function, and should be re-assessed during treatment if any worsening is suspected. When Pradaxa is used long term in patients with non-valvular atrial fibrillation, or when it is used in patients with DVT or PE, kidney function should be assessed at least once a year if their kidney function is mildly to moderately reduced or if they are over 75 years old.

For further information, see the summary of product characteristics (also part of the EPAR).

How does Pradaxa work?

Patients undergoing hip or knee replacement surgery are at a high risk of blood clots forming in their leg veins. These clots, which include deep vein thrombosis (DVT), can be dangerous if they move to another part of the body such as the lungs. Patients who have atrial fibrillation are also at risk of blood clots which can travel to the brain and cause a stroke.

The active substance in Pradaxa, dabigatran etexilate, is a ‘prodrug’ of dabigatran. This means that it is converted into dabigatran in the body. Dabigatran is an anticoagulant, meaning that it prevents the blood from coagulating (clotting). It blocks a substance called thrombin, which is central to the process of blood clotting.

How has Pradaxa been studied?

Two main studies have been performed to compare Pradaxa (either 220 or 150 mg a day) with enoxaparin (another anticoagulant) in patients who had undergone a hip or knee replacement. The first study involved a total of 2,101 patients who had had a knee replacement operation, and the second involved a total of 3,494 patients who had had a hip replacement. In both studies, the main measure of effectiveness was based on the number of patients who had blood clots forming in the veins or who died of any cause during the treatment period. In most cases, blood clot formation was detected using scans of the veins or by looking for signs of blood clots in the lungs.

A third main study compared Pradaxa (110 mg and 150 mg twice a day) with warfarin (another anticoagulant) in around 18,000 adult patients with non-valvular atrial fibrillation who were considered to be at risk of stroke. The patients were treated for one to three years and the main measure of

effectiveness was based on the proportion of patients who had a stroke or a blood clot blocking blood vessels in other parts of the body each year.

Two main studies in over 5,100 adult patients with symptoms of DVT or PE, and who were initially treated with an injectable anticoagulant, compared Pradaxa with warfarin. Another two studies looked at the prevention of VTE or PE in around 4,200 adult patients with symptoms of recurring blood clots and who were on long-term treatment with anticoagulants. One of these prevention studies compared Pradaxa with warfarin and the other compared Pradaxa with placebo (a dummy treatment). The main measure of effectiveness for these four studies was based on the number of patients who had blood clots forming in the veins (DVT) or lungs (PE), or who died from cardiovascular causes during the treatment period.

What benefit has Pradaxa shown during the studies?

Pradaxa was as effective as enoxaparin in preventing the formation of blood clots or death. In the study of patients undergoing knee replacement, blood clots were detected in 36% of the patients taking the 220 mg dose of Pradaxa (182 out of 503), compared with 38% of the patients receiving enoxaparin (192 out of 512). There was one death in each group (less than 1%).

In the study of patients undergoing hip replacement, blood clots were detected in 6% of the patients taking 220 mg Pradaxa (50 out of 880), compared with 7% of the patients receiving enoxaparin (60 out of 897). Three patients in the Pradaxa group died (less than 1%), but two of these deaths were unrelated to blood clots. In the hip and knee studies, there was some evidence that the 220 mg dose may be more effective than the 150 mg dose.

The study in patients with non-valvular atrial fibrillation showed that the proportion of patients who had a stroke or other problems caused by blood clots each year was around 1.5% for patients taking Pradaxa 110 mg (183 patients out of 6,015) and 1.1% for patients taking Pradaxa 150 mg (134 out of 6,076), compared with 1.7% for patients taking warfarin (202 out of 6,022).

In the studies looking at treatment of VTE and PE, blood clots or blood-clot related death occurred in 2.7% (68 out of 2553) of patients treated with Pradaxa, compared with 2.4% (62 out of 2554) of patients treated with warfarin.

In the first study looking at prevention of VTE and PE, blood clots or blood-clot related death occurred in 1.8% (26 out of 1430) of patients treated with Pradaxa, compared with 1.3% (18 out of 1426) of patients treated with warfarin. In the second prevention study, blood clots or blood-clot related death occurred in 0.4% (3 out of 681) of patients treated with Pradaxa, compared with 5.6% (37 out of 662) of patients treated with placebo.

What is the risk associated with Pradaxa?

The most common side effect with Pradaxa (seen in more than one patient in 10) is bleeding. For the full list of all side effects reported with Pradaxa, see the package leaflet.

Pradaxa must not be used in patients who have severely reduced kidney function, who are currently bleeding significantly or who have a condition putting them at significant risk of major bleeding. It must not be used in patients taking any other anticoagulant medicine, except in specific situations such as when the anticoagulant medication is being switched. Pradaxa must also not be used in patients with serious liver problems or patients taking by mouth or injection the medicines ketoconazole and itraconazole (used for fungal infections), ciclosporin (a medicine used to reduce the activity of the immune system) or dronedarone (a medicine to treat a heart problem called atrial fibrillation). For the full list of restrictions, see the package leaflet.

Why has Pradaxa been approved?

The CHMP considered that the benefits of the medicine outweigh its risk and recommended that it be given marketing authorisation. The CHMP noted that effect of Pradaxa in preventing the formation of blood clots patients who have undergone a hip or knee replacement is comparable to that of enoxaparin. Pradaxa, which is taken by mouth, has the advantage of being more convenient for patients.

The CHMP also noted that Pradaxa compared well with warfarin in reducing the risk of strokes in patients with atrial fibrillation without increasing the risk of major bleeding. Since certain patients are at increased risk of bleeding, a number of precautions were included in the prescribing information.

In addition, the CHMP noted that the overall benefit of Pradaxa in the treatment and prevention of DVT and PE is comparable to that of warfarin. However, the number of bleeding events was lower for Pradaxa than for warfarin. Although the studies showed a small higher risk of heart problems with Pradaxa than with warfarin, the benefits of Pradaxa were still considered to outweigh its risks.

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

A risk management plan has been developed to ensure that Pradaxa is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Pradaxa, including the appropriate precautions to be followed by healthcare professionals and patients.

In addition, the company that makes Pradaxa will provide an educational pack for all doctors who are expected to prescribe the medicine, to increase awareness of the risk of bleeding and provide guidance on how to manage it. Patients will also receive an alert card summarising key safety information on the medicine.

Other information about Pradaxa

The European Commission granted a marketing authorisation valid throughout the European Union for Pradaxa on 18 March 2008.

The full EPAR for Pradaxa 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 Pradaxa, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 01-2015.