The National Institute for Health and Clinical Excellence (NICE) has approved the use of dabigatran etexilate (Pradaxa) as a treatment option for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation\(^*\) with one or more of the following risk factors: previous stroke, transient ischaemic attack (TIA) or systemic embolism; left ventricular ejection fraction below 40\%; symptomatic heart failure (>NYHA II); age 75 years; age 65 years with one of the following: diabetes mellitus, coronary artery disease or hypertension.

**Background**

The risk of stroke is a major concern for people with atrial fibrillation, and stroke severity is usually greater in this group than in people who have strokes from other causes. From the doctor’s perspective Warfarin can be problematic since many patients are outside their target therapeutic INR range at any one time, and many patients dislike it since there are many drug and food interactions, and regular monitoring by blood tests (INR) is required, which can of course impact on work and family life. Dabigatran on the other hand does not require monitoring and has few drug interactions.

**The evidence**

The main evidence for clinical effectiveness came from the RE-LY study, which took place in 44 countries including the UK. A total of 18,113 people were enrolled across the three treatment arms in a 1:1:1 ratio. People recruited into the study were randomly allocated to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily or warfarin. The reduction in relative risk of stroke or systemic embolism compared with warfarin was 10\% for dabigatran 110 mg and 35\% for dabigatran 150 mg. Dabigatran 150 mg twice daily was associated with a significantly lower incidence of stroke, systemic embolism or vascular mortality compared with warfarin. There were no statistically significant differences between dabigatran 110 mg twice daily and warfarin in the incidence of stroke or systemic embolism, ischaemic stroke or vascular mortality. However, in people with good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with switching to dabigatran. There was a statistically significant reduction in the incidence of haemorrhagic stroke and life-threatening bleeds, but an increase in gastrointestinal bleeding for both doses of dabigatran compared with warfarin.

**Contraindications**

Dabigatran is contraindicated in people with severe renal impairment, active clinically significant bleeding, organic lesions at risk of bleeding, impairment of blood clotting, and impairment of the liver or liver disease expected to have an impact on survival.

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Drug interactions and side-effects

Concomitant treatment with a group of drugs called strong P-gp inhibitors, which include ketoconazole, cyclosporine, itraconazole and tacrolimus, is contraindicated, as these can cause dabigatran levels in the blood to rise. Caution should be exercised with other drugs such as amiodarone, quinidine, verapamil and clarithromycin for the same reason. Rifampicin, St John’s wort, carbamazepine, phenytoin and other strong P-gp inducers should also be avoided, since they will lower the plasma concentration of dabigatran.

The most common adverse events in people receiving dabigatran are anaemia, abdominal pain, diarrhoea, dyspepsia, gastrointestinal bleeding, genitourinary bleeding (patients may notice blood in their urine), nausea and nose bleeds. For full details of side effects and contraindications, see the summary of product characteristics.

Warfarin or dabigatran?

NICE states that the decision about whether to start treatment with dabigatran should be made after an informed discussion between the doctor and the patient about the risks and benefits of dabigatran compared with warfarin. For patients already taking warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of INR control.

A forgotten dose of dabigatran may still be taken up to 6 hours prior to the next scheduled dose. There is no specific antidote to dabigatran, unlike with warfarin, which can be antagonised by vitamin K.

Dabigatran is marketed as Pradaxa by Boehringer Ingelheim. The manufacturer also provides Patient Alert Cards which patients are advised to carry with them at all times. The drug must be stopped in advance of surgical or other invasive procedures due to the risk of bleeding.

Dose

Dabigatran is available as 110 mg and 150 mg capsules and comes in packs of 60 capsules. The manufacturer has stated that the cost to the NHS of a pack of 60 capsules of either dabigatran 110 mg or 150 mg will be £75.60 (excluding VAT).

The dose should be reduced to 110mg twice daily in patients taking verapamil.

The recommended daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. Therapy is continued in the long term. For patients aged 75–80 years, a dose of 220 mg taken as one 110 mg capsule twice daily can be considered at the discretion of the physician for individual patients whose thromboembolic risk is low and bleeding risk is high. Patients aged 80 years or older should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily because of the increased risk of bleeding in this population.

Availability on the NHS

The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment or other technology, the NHS must usually provide funding and resources for it within three months of the guidance being published. If the Department of Health issues a variation to the three-month funding direction, details will be available on the NICE website.

* National Institute for Health and Clinical Excellence

Final appraisal determination – Dabigatran etexilate for the prevention of stroke and systemic