Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS023
Dabigatran (Pradaxa®) for Stroke prevention in Atrial Fibrillation	August 2018

VERDICT

Dabigatran, within its licensed indications and in line with NICE TA249, is recommended as an option for the prevention of stroke in non-valvular AF and should be initiated by a specialist, tailored to the clinical situation of the patient. Follow on prescribers should receive a checklist from the initiating specialist indicating that the patient is suitable for dabigatran therapy and has received appropriate guidance from the specialist. If the checklist is not made available, follow on prescribing in primary care should not commence until the specialist has been contacted and a checklist obtained.

For Primary Care Prescribers: The committee recognises the beneficial effect of anticoagulant therapy once a diagnosis of AF has been made in primary care. In this instance, dabigatran may be initiated by a primary care prescriber where they have attended a suitable training course and can demonstrate expertise in managing anticoagulant therapy. The committee also advise that the specialist initiated drug checklist is also completed by the primary care prescriber.

Specialist Drugs Status: Specialist Advised (SA)

SUMMARY NOTES[1]

Indication: Prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation with one or more of the following risk factors:
Previous stroke, transient ischemic attack, or systemic embolism
Left ventricular ejection fraction < 40 %
Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
Age ≥ 75 years
Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

Presentation: Pradaxa® 110 mg and 150 mg capsules

Dose: The recommended daily dose is 300 mg taken as one 150 mg capsule twice daily.
Patients between 75 - 80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.

Avoid in patients with a calculated Creatinine Clearance (using Cockcroft-Gault Equation) < 30mL/minute.
Monitor renal function at least annually.

Cost Comparison: cost per 28 days (eMIMs, Drug Tariff August 2018)

Dabigatran	150 mg or 110 mg bd	£47.60
Rivaroxaban	20 mg daily	£50.40
Apixaban	5 mg bd	£53.20
Edoxaban	30 – 60 mg daily	£49.00
Warfarin	5 mg daily	£0.61 (variable depending on INR; costs including monitoring, range widely depending on local arrangements from £220 to £480

DRUG PROFILE

The pivotal study for dabigatran is RE-LY. RE-LY[2] was a randomised controlled trial designed to compare two doses of dabigatran (110 mg and 150 mg twice daily) with warfarin in 18 113 people with non-valvular AF (NVAF) and at least one stroke risk factor (mean CHADS2 = 2.1). Comparison between warfarin and dabigatran was not double blind given the need to allow warfarin dose adjustments; comparison between dabigatran doses was double blind. The primary endpoint was a composite of prevention of stroke (ischaemic or haemorrhagic) and systemic embolism. At median two-year follow-up, **dabigatran 110 mg was non-inferior to warfarin for the primary endpoint (**1.54% per year vs. 1.71% per year respectively, $p < 0.001$), **whilst the higher dose (150 mg twice daily) was found to be statistically superior** (1.11% per year vs. 1.71% per year, $p < 0.001$).

DRUG PROFILE cont'd

For all-cause mortality there was no statistically significant difference between the groups; death from vascular causes was statistically significantly lower for dabigatran at the 150 mg dose compared to warfarin (2.28% vs. 2.69% per year, p = 0.04). Gastrointestinal bleeding was reported more often for dabigatran 150 mg than warfarin (1.56% vs. 1.07% per year, p < 0.001). A recent UKMI[3] and a further new drugs evaluation[4] document gives further detail and evaluation of the RE-LY study. A further UKMI briefing paper [5] provides a summary of the key issues associated between dabigatran and rivaroxaban.

In December 2011, the MHRA[6] issued advice on renal monitoring following a number of cases of serious and fatal haemorrhage reported in elderly patients with renal impairment who were receiving dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (calculated creatinine clearance <30 mL/min)[1]. Dabigatran is also contraindicated in people with active clinically significant bleeding, organic lesions at risk of bleeding, impairment of haemostasis, and hepatic impairment or liver disease expected to have an impact on survival.

Concomitant treatment with systemic ketoconazole, dronedarone, ciclosporin, itraconazole or tacrolimus is also contraindicated[1]. The most common adverse events in people receiving dabigatran are anaemia, abdominal pain, diarrhoea, dyspepsia, gastrointestinal haemorrhage, genitourinary haemorrhage (patients may notice blood in their urine), nausea and nose bleeds[1].

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE)[7] Dabigatran is **recommended** as an option, within its licensed indication, in people with **non-valvular atrial fibrillation** with one or more of the following **risk factors**:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

It is recommended that the treatment initiation decision includes a discussion of the **risks and benefits of dabigatran compared with warfarin**. It is also suggested that for patients who are already taking warfarin, the potential **risks and benefits of switching** to dabigatran are discussed with **consideration** of their level of **international normalised ratio** (INR) **control**.

Scottish Medicines Consortium (SMC)[8] Dabigatran has been accepted for use in NHS Scotland in prevention of stroke and systemic embolism in adult patients with non valvular AF with risk factors as defined in the SPC.

Midlands Therapeutics Review and Advisory Committee (MTRAC)[9] Category A(Q3) – Stronger evidence, lower place in therapy.
Dabigatran is suitable for prescribing in primary care as a second-line treatment option only if a patient's INR cannot be stabilised adequately within the target range over the longer term with a suitable trial of optimised warfarin treatment. Whilst the evidence for efficacy for dabigatran was strong, the considerable cost impact associated with commissioning this drug and concerns around monitoring, adherence to treatment and long-term safety gave dabigatran a low place in therapy.

MTRAC Commissioning considerations[9] The committee recommends that warfarin remains the first-line option for anticoagulation in patients with AF at high risk of a stroke. Commissioners should ensure optimal use of existing warfarin therapy services including access to INR clinics, use of computerised decision-support software, and access to drugs such as acenocoumarol for patients who are allergic to warfarin.

In view of the considerable financial implications, dabigatran treatment should only be prescribed for:

- those patients with co-morbidities who are adherent to warfarin monitoring and lifestyle requirements but need frequent co-prescribed medications that interact with warfarin and affect the patients' time in therapeutic range (TTR)
- those patients who are adherent to monitoring and lifestyle requirements but whose TTR remains unacceptable despite attempts to optimise treatment with warfarin. Commissioners should set the TTR threshold at an affordable level for their local Health Economy.

References

1. SPC Dabigatran (Pradaxa®). Boehringer Engelheim Ltd . 7/6/18. Available from www.medicines.org.uk
2. Connolly SJ, Ezekowitz MD et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2009; 361: 1139-51 http://www.nejm.org/doi/full/10.1056/NEJMoa0905561
3. UKMI London New Drugs group. APC/DTC Briefing document. Dabigatran for stroke prevention in patients with atrial fibrillation. August 2011
4. UKMI NYRT DTC New drugs evaluation . Dabigatran in atrial fibrillation. No. 111 October 2011
5. UKMI London New Drugs Group. A briefing paper on dabigatran and Rivaroxaban. January 2012
6. MHRA Drug safety update. Dabigatran: risk of serious haemorrhage-need for renal function testing. December 2011
7. NICE TA249. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. August 2011 Accessed https://www.nice.org.uk/guidance/ta249
8. SMC. Dabigatran Pradaxa 672/11 November 2011
9. Dabigatran for stroke prevention in Atrial fibrillation. Midlands Therapeutics Review and Advisory Committee. 2012. Commissioning guidance. https://ccg.centreformedicinesoptimisation.co.uk/download/cc521ad89f98500fb0801c931a967306/Dabigatran-Summary-Jun-12.pdf