APPENDIX F

NHS Surrey

Surrey and Sussex NHS Healthcare NHS Trust

WORKING IN PARTNERSHIP WITH

Information sheet

Dabigatran (Pradaxa®)110mg and 150mg Tablets

FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

Surrey Prescribing Clinical Network classification: **Green**

A consensus group met on 9th May 2012 to make recommendations around the use of new oral anticoagulants (dabigatran and rivaroxaban) for stroke prevention in atrial fibrillation. It was agreed that initiation of these drugs would be appropriate in primary care and given a **GREEN** status on the Traffic Light System. It was also felt that an information sheet would be useful in instances where these drugs were not initiated in primary care to ensure that agreed discussions with patients have occurred to ensure a consistent approach across the healthcare economy. This information sheet is available on the internet (http://www.app.surreyhealth.nhs.uk/gpview/default.html) forming part of Surrey PCT's Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter.

RESPONSIBILITIES and ROLES

Surrey Prescribing Clinical Network (PCN) recommendation
• The focus of AF management should be to identify patients with AF and undertake stroke risk assessment using the $CHADS_2$ or CHA_2DS_2–VASc risk assessment tool. Patients with a $CHADS_2$ score ≥ 2 or $CHADS_2$ score 1 and considered high risk should be initiated on warfarin in the first instance, unless contraindicated • Warfarin remains the agent of choice for the prevention of stroke and systemic embolism in AF. Patients currently stable on warfarin therapy should not be considered for a switch to a new oral anticoagulant • Warfarin anticoagulant services should be reviewed to ensure they deliver a high quality standard of care and meet the needs of patients who have difficulty complying with the specific monitoring requirements of warfarin therapy • New oral anticoagulants (NOACs) should be considered as an alternative to warfarin for stroke prevention in AF in patients who: ○ have a warfarin allergy or have an absolute contraindication to warfarin ○ have an ischaemic stroke whilst stable on warfarin and other treatment options including increasing the INR target range or adding in antiplatelets have been considered ○ are intrinsically unstable on warfarin after an adequate trial (usually at least 3 months) despite: - being adherent to warfarin monitoring and lifestyle requirements AND - evidence of compliance with drug therapy AND - attempts have been made to optimise warfarin treatment e.g. patients with co-morbidities requiring frequently co-prescribed medications that interact with warfarin • Aspirin (with or without clopidogrel) is not a suitable alternative to warfarin or NOACs in patients with atrial fibrillation and CHADS2 score ≥ 2, as it offers significantly less protection against stroke. Aspirin (with or without clopidogrel) should only be considered for such patients where warfarin and NOACs cannot be used due to allergy or contraindications
Responsibilities of initiating clinician
1. Dabigatran should only be recommended in line with the PCN recommendation above 2. In making the recommendation the initiating clinician must ensure that an informed discussion with the patient and/or their carer has been conducted covering the risks and benefits of prescribing dabigatran compared with warfarin or other anticoagulants for stroke prevention in atrial fibrillation.
Patient's / Carer's roles
1. Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment. 2. Share any concerns in relation to the treatment. 3. Tell the specialist or GP of any other medication being taken, including over-the-counter products. 4. Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP.

Supporting Information - This information sheet does not replace the SPC[1], which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF[2].

www.medicines.org.uk

Dabigatran is a black triangle drug - any adverse effects must be reported to the MHRA

Licensed indications

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism (SEE)
- 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

Dosage and administration

Age / Renal Function/ Concomitant Medication	Recommended Dose	Comments
ADULT over 18 years	150mg bd	Consider 110mg bd if high bleeding risk or GI irritation
ELDERLY 75 – 80 years	150mg bd	If at low thromboembolic risk but high bleeding risk consider 110mg bd
ELDERLY > 80years	110mg bd	
Renal function < 30 mL/min CrCL	**Contraindicated**	
Moderate renal impairment (CrCL 30-50 ml/min)	150mg bd	Consider 110mg bd if high bleeding risk or GI irritation
Concomitant Verapamil	110mg bd	

MISSED DOSE

- A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.
- No double dose should be taken to make up for missed individual doses.

METHOD OF ADMINISTRATION

- Capsules should be swallowed as a whole with water, with or without food.
- Must be retained in original packaging so unsuitable for compliance systems unless kept in its unopened blister
- Patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) as oral bioavailability may be increased by up to 75%

Contraindications and Cautions

Contra-indications	Cautions
• Active clinically significant bleeding • Organic lesion at risk of bleeding • Spontaneous or pharmacological impairment of haemostasis • Patients with severe renal impairment (CrCL < 30 ml/min) • Hepatic impairment (elevated liver enzymes > 2 upper limit of normal (ULN)) or liver disease expected to have any impact on survival • Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus • Hypersensitivity to the active substance or to any of the excipients • Pregnancy or within 48 hrs post partum • Dabigatran must not be used in patients using any other anticoagulant, unless the patient is being switched to or from dabigatran[3]	• Body-weight less than 50 kg • Recent surgery • Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs) • Bacterial endocarditis (increased risk of bleeding) • Bleeding disorders • Active gastro-intestinal ulceration • Assess renal function before treatment in all patients and at least annually in elderly and patients with renal impairment • Concomitant use of drugs that increase risk of bleeding
Drug Interactions: See overleaf for details of drug interactions including contraindicated drug therapies	

Side Effects - See BNF/SPC for full details

The most common adverse effects of dabigatran are nausea, dyspepsia, diarrhoea, abdominal pain, anaemia, haemorrhage*; less commonly* hepatobiliary disorders, vomiting, dysphagia, gastro-intestinal ulcer, gastro-oesophageal reflux, oesophagitis, thrombocytopenia

Special warnings and precautions for use

a) Haemorrhagic risk

The most commonly reported adverse reactions in the pivotal studies are bleedings occurring in total in approximately 16.5%. Although low in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes

Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia). Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding

Factors, such as decreased renal function (30-50 ml/min CrCL), age ≥ 75 years, low body weight < 50 kg, or strong P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels

There is no specific antidote to dabigatran. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the clinician's discretion.

b) Hepatic Effects

Patients with elevated liver enzymes > 2 ULN were excluded from the study investigating the prevention of stroke and SEE associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran is not recommended in this population

c) Renal Effects

Renal function should be assessed by calculating the CrCL prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment. Treatment with dabigatran in patients with severe renal impairment (creatinine clearance (CrCL) < 30 ml/min) is contraindicated.

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of dabigatran is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran to 220 mg taken as one 110 mg capsule twice daily should be considered. Close clinical surveillance is recommended in patients with renal impairment.

While on treatment renal function should be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain co-medications, etc).

d) Myocardial Infarction

In the phase III study RE-LY the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

Drug Interactions – Please see BNF/SPC for full details

Interacting Drug / Drug Class	Details and Action to be Taken
Ketoconazole Cyclosporin Itraconazole Tacrolimus	Increase plasma concentration of dabigatran. Use contraindicated with dabigatran
Verapamil	Plasma concentration of dabigatran possibly increased by verapamil. Reduce dabigatran to 110mg bd
Amiodarone Quinidine Clarithromycin	Plasma concentration of dabigatran increased by amiodarone (BNF advise reduce dose of dabigatran etexilate). Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped. SPC states that concomitant administration of other strong P-gp inhibitors (such as quinidine and clarithromycin) is expected to result in increased dabigatran plasma concentrations, but not listed as an interaction in Appendix 1 of the BNF (March 2012)
Dronedarone	Plasma concentration of dabigatran etexilate increased by dronedarone—avoid concomitant use
Rifampicin St John's Wort Carbamazepine Phenytoin Ritonavir	May reduce dabigatran blood levels. Avoid concomitant use.
Anticoagulants	Risk of bleeding increased. Avoid concomitant use of other anticoagulants. No parental anticoagulant should be given for 12 hours after last dose of dabigatran
Antiplatelet drugs	Risk of bleeding increased. This bleeding risk increase is similar to concomitant use of antiplatelet drugs with warfarin.

NSAIDs / Aspirin	Possible increased risk of bleeding when dabigatran etexilate given with NSAIDs
Sulfinpyrazone	Possible increased risk of bleeding when dabigatran etexilate given with sulfinpyrazone
SSRIs / SNRIs	Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)

References

1 SPC Pradaxa® (Dabigatran) Boehringer Ingelheim 2012 Accessed May 23rd 2012 at http://www.medicines.org.uk/EMC/medicine/24839/SPC/Pradaxa+150+mg+hard+capsules/

2 BNF, March 2012

3 EMA Press release 25/05/2012 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/05/news_detail_001518.jsp&mid=WC0b01ac058004d5c1