

Protocol for use of Dabigatran etexilate

Therapeutic indication

Dabigatran etexilate capsule (Pradaxa[®] made by Boehringer-Ingelheim), is a direct thrombin inhibitor licensed in the UK for the primary prevention of venous thromboembolism in adult patients after **elective total hip replacement or total knee replacement surgery**. It should not be used in other patients until the licence is extended.

KGH Medicines Management Clinical Committee has approved the use of dabigatran in these groups of patients. These patients will undergo risk assessment for the use of oral thromboprophylaxis, and those suitable for its use will be provided with the total duration of medication at discharge.

Pharmaceutical preparation

Light blue and cream hard opaque capsules; 110mg capsules are imprinted with "R110"
75mg capsules are imprinted with "R75"

TTA packs are available on Ashton ward of the following:

- 110mg x 60 capsules: for hip replacement patients (pack of 60 capsules)
- 75mg x 60 capsules: for hip replacement patients (pack of 60 capsules)
- 110mg x 20 capsules: for knee replacement patients (two packs of 10 capsules)
- 75mg x 20 capsules: for knee replacement patients (two packs of ten capsules)

Recommended dose of dabigatran

Initial dose 110mg po as a single dose (one capsule of 110mg) 1 - 4 hours after surgery
Subsequent doses 220 mg po once daily (two capsules of 110mg)

Label on the TTA packs are:

- Hip replacement patients: Take ONE capsule 1 to 4 hours after surgery, then take TWO capsules once daily for 29 days.
- Knee replacement patients: Take ONE capsule 1 to 4 hours after surgery, then take TWO capsules once daily for 9 days.

The capsule should be swallowed whole with water, with or without food. The last remaining capsule should be discarded at the end of the course.

No dosage adjustments are recommended but there is limited experience in use of dabigatran in patients under 50kg or over 110kg body weight.

Reduced doses are given in some patients:

Dabigatran 75mg 1 - 4 hours after surgery followed by 150mg daily is recommended in:

- **Moderate renal impairment:** (creatinine clearance 30-50ml/min.)
- **Elderly patients >75 years**
- **Patients on amiodarone**
- **Mild thrombocytopenia:** platelet count 50-100x10⁹/l.

Careful clinical monitoring is recommended, as there is limited experience of the use of dabigatran in these patients.

Active bleeding or high-risk of bleeding

Delay initial dose until haemostasis is secured. If treatment is not started on the day of surgery, then treatment should be initiated with 150mg/220mg (2 capsules) once daily from the following day.

Duration of treatment

After hip replacement: a total of 30 days from the date of surgery

After knee replacement: a total of 10 days from the date of surgery

Extended duration of treatment: dabigatran is currently licensed for 28 to 35 days after total hip replacement and 10 days after total knee replacement. If extended off licence use is considered it should be for a specific patient who remains at high risk of venous thrombosis at the end of the licensed duration listed above, with consultant authorization for a clearly specified period of days, eg patients who are slow to regain mobility or have previous post-thrombotic venous damage and would otherwise continue on extended duration LMW heparin.

At pre-op assessment clinic, include the following:

- Routine recording of any history or family history of excess bleeding or thrombosis.
- Blood tests for **FBC, group & save, LFTs, U&E & eGFR**. The results must be examined and signed by a doctor when the patient is admitted, before dabigatran is prescribed. File the results in patient's notes.
- Routine recording of drugs being taken, with particular note of any that might affect use of dabigatran (see drug interactions).

Patients on aspirin, clopidogrel or dipyridamole:

- Patients undergoing total hip and total knee replacement surgery and already pre-operatively on long term aspirin and/or clopidogrel and/or dipyridamole, must stop these tablets one week prior to surgery.
- Restart these anti-platelets when the course of Dabigatran has been completed after surgery. Unless the patient is considered to be at high risks of clots, in which case, the doctor should review the patient and consider the benefits and risks of continuing these medications along with Dabigatran.

Patients on long term warfarin pre-operatively:

- Stop warfarin 4 days before surgery
- Start low molecular weight heparin (LMWH) enoxaparin 1.5 mg/kg every 24 hour by subcutaneous injection. If CrCl < 30ml/min, reduce dose to 1mg/kg once daily.
- Stop LMWH 24 hours prior to surgery
- Check INR level prior to surgery to ensure it is below 1.5
- Resume LMWH 12 hours post operatively
- Resume warfarin on the day of surgery
- Check INR level and dose warfarin daily until pre-operative recommended level of INR is achieved.
- Stop LMWH when required INR level achieved and continue with pre-operative warfarin regime.
- Please note: patients on warfarin/ enoxaparin do not need to take dabigatran.

Contraindications. Dabigatran is contraindicated in patients with:

- **Active clinically significant bleeding.** Delay initial dose until haemostasis is secured.

- **Organic lesion at risk of bleeding** e.g. active ulcerative gastrointestinal disease, recent biopsy or major trauma, stroke, brain, spinal or ophthalmic surgery, bacterial endocarditis.
- **Bleeding tendency** (eg INR >1.4 due to liver disease, thrombocytopenia - platelet count <50x10⁹/l, congenital or acquired coagulation defect)
- **Severe renal impairment** (CrCl <30ml/min), use alternative thromboprophylaxis.
- **Hepatic impairment** with elevated liver enzymes (ALT >2x upper limit of normal). Patients with mildly elevated liver enzymes (ALT<2x upper limit of normal) can take full doses of dabigatran.
- **Known hypersensitivity** to one of the active substances or components in the preparation
- **Concomitant drug treatment** with quinidine, anticoagulants or most anti-thrombotics (see drug interactions).
- **Indwelling epidural catheter** or within 2 hours of removal of epidural catheter.
- **Children & adolescents** below 18 years old should not take dabigatran due to lack of data on safety & efficacy
- **Pregnant or breast-feeding mothers** should not take dabigatran due to lack of data on safety & efficacy.

Close clinical surveillance (looking for signs of thrombosis, bleeding or anaemia) is recommended throughout the treatment period, particularly if dabigatran is given to a patient whose clinical condition is not in the list of contraindications above, but who has a potentially increased risk of thrombosis or haemorrhage. Diseases associated with an increased risk of bleeding are conditions such as congenital or acquired coagulation disorders, active ulcerative gastrointestinal disease, recent biopsy or major trauma, recent intracranial or brain, spinal or ophthalmic surgery, bacterial endocarditis etc.

Drug interactions as listed from manufactures literature

Please consult SPC for Pradaxa[®] (dabigatran) for further information.

- **Amiodarone:** reduce dose of dabigatran to 150 mg daily if patient is taking amiodarone.
- **Anticoagulants:** do not give dabigatran with warfarin or other vitamin K antagonists, heparin**, low molecular weight heparin (LMWH), heparin derivatives, danaparoid or thrombolytics.
 - ** Unfractionated heparin in the low doses needed to maintain a central venous or arterial catheter is acceptable.
- **Other antithrombotics:** do not give dabigatran to patients on clopidogrel, ticlopidine or GPIIb/IIIa receptor antagonists such as abciximab. If switching from LMWH, the first dose of Dabigatran should be given 24 hours after the last therapeutic dose. If switching to LMWH, first dose of therapeutic LMWH should be given 24 hours after last dose of Dabigatran.
- **Aspirin & COX-2 inhibitors:** concomitant administration of low dose aspirin (less than 160mg daily) with dabigatran and of COX-2 inhibitors such as celecoxib and meloxicam was allowed in the research trials and can therefore be co-prescribed if clinically indicated, with careful clinical monitoring. Bleeding risk may be increased.
 - Please note the specific recommendation made by the orthopaedic team above with regard to stopping and starting aspirin.
- **P-glycoprotein inhibitors:**
 - Quinidine:** see contraindications list. LMWH prophylaxis is recommended.
 - Verapamil, clarithromycin** and other P-glycoprotein inhibitors: no dosage advice is given but there is very little clinical experience of concomitant use of these drugs with dabigatran and caution is therefore advised.
- **P-glycoprotein inducers:**
 - Rifampicin:** reduced dabigatran effect possible, but no dosage advice is given. Caution is therefore advised.
 - St Johns Wort:** this may reduce the anti-thrombotic effect of dabigatran so should be stopped peri-operatively.

- **Diclofenac, ibuprofen and other anti-platelet NSAIDs:** there will be an increased risk of GI haemorrhage if these drugs are administered to patients on dabigatran, therefore an alternative should be used when possible. Careful clinical monitoring for signs of bleeding is essential if they are used.

Monitoring

Dabigatran is not a Vitamin K antagonist and **its anticoagulant effect does not require routine monitoring**. INR and Prothrombin Time (PT) may be elevated in patients on dabigatran and should not be used as a measure of the anticoagulant effect of Dabigatran. aPTT is elevated in a non-linear fashion in patients on Dabigatran.

Adverse effects of dabigatran

- Bleeding (likely in 14%, with major bleeds in 1.8%, some immediately post-operatively)
- Abnormal LFTs (ALT increased in <1% as with LMWH; no serious abnormalities)
- Hypersensitivity to dabigatran or to any of the excipients in the preparation (very rare)

Please consult the SPC for Pradaxa® (dabigatran) for further information.

Overdose

There is no antidote to dabigatran.

Coagulation test results are not known to correlate with clinical effect.

Dabigatran level achieve a peak at 2 - 4 hours after oral dose; mean half-life of drug after surgery is 14-17 hours. This is independent of the dose.

Management of patients with suspected overdose:

- Stop dabigatran
- Monitor bleeding carefully.
- Check FBC, creatinine, LFTs and coagulation screen.
- Maintain diuresis (as dabigatran is predominantly renal excretion)
- Investigate and treat any bleeding promptly
- Ensure surgical haemostasis is adequate
- Liaise with Haematology doctor for advice.
- FFP may be helpful if there is significant bleeding within 12 hours of an overdose
- Please discuss such case with Consultant Haematologist for further advice, as Recombinant FVIIa may be required for severe bleeding.
- Dialysis will remove the drug from circulation but no clinical data is available.

References

1. Eriksson, B.I., Dahl, O.E., Rosencher, N., Kurth, A.A., van, D.C.N., Frostick, S.P., Kälebo, P., Christiansen, A.V., Hantel, S., Hettiarachchi, R., Schnee, J., Büller, H.R. & Group, R.-M.S. (2007) Oral dabigatran etexilate vs subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the Journal of thrombosis and haemostasis : JTH, 5, 2178-2185
2. Eriksson, B.I., Dahl, O.E., Rosencher, N., Kurth, A.A., van, D.C.N., Frostick, S.P., Prins, M.H., Hettiarachchi, R., Hantel, S., Schnee, J., Büller, H.R. & Group, R.-N.S. (2007) Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet*, **370**, 949-956.
3. Liesenfeld, K.H., Schäfer, H.G., Trocóniz, I.F., Tillmann, C., Eriksson, B.I. & Stangier, J. (2006) Effects of the direct thrombin inhibitor dabigatran on ex vivo coagulation time in orthopaedic surgery patients: a population model analysis. *British journal of clinical pharmacology*, **62**, 527-537

4. SPC for Pradaxa® (dabigatran). Date of revision of text 25/03/2009. Access via <http://emc.medicines.org.uk/>

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