NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA157; Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults

This guidance was issued in September 2008.
The review date for this guidance is June 2011.

1. Recommendation

- The guidance should be transferred to the 'static guidance list'.
- That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of dabigatran etexilate within its licensed indication for the prevention of venous thromboembolism after elective hip or knee replacement surgery in adults.

3. Current guidance

1.1. Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

4. Rationale[1]

Since TA157 was issued, NICE has published a clinical guideline CG92 'Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery'. Although the clinical guideline does not reproduce the wording of TA157 verbatim, the recommendation has been effectively incorporated in that dabigatran is included in the list of options for pharmacological VTE prophylaxis after surgery in both elective hip and elective knee replacement. There is no new evidence to suggest that this recommendation should change.

Moving TA157 to the static list means that the Technology Appraisal guidance will remain extant alongside the clinical guideline. This has the effect of preserving the funding direction. The review decision date for the clinical guideline is January 2013. If it is decided that the clinical guideline should be reviewed, then a new proposal for TA157 can be developed during the pre-scoping stages of that guideline.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

5. Implications for other guidance producing programmes

This section is for representatives of other guidance producing centres (e.g. CPP CPHE) to present their view if the proposal overlaps with a proposed or ongoing project of theirs.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from February 2008 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Since the guidance was published, there has been a minor amendment to the SPC for dabigatran etexilate to state that for people receiving verapamil a reduced dose of 150 mg (75 mg starting dose, 150 mg continuing dose) is recommended.

The price has not changed since the publication of the guidance.

The original guidance compared the use of dabigatran etexilate (at 150 mg and 220 mg daily doses) with enoxaparin, a low molecular weight heparin (LMWH), using direct evidence from randomised controlled trials (RCTs), and with fondaparinux, using RCT evidence which had been incorporated into a mixed-treatment comparison.

The original guidance recommended that further pragmatic trials of dabigatran etexilate compared with LMWH in both total hip replacement and total knee replacement should be undertaken as they would serve to lessen the uncertainty surrounding the effectiveness and cost effectiveness of these treatments. The guidance also recommended that head-to-head trials of dabigatran etexilate compared with fondaparinux should be undertaken as this would strengthen the evidence base for this comparison.

The updated literature search identified a number of publications which reported comparisons of dabigatran etexilate with enoaxaparin which were published after the guidance was issued. A systematic review and meta analysis (Wolowacz et al. 2009) concluded that dabigatran etexilate at a dose of 220mg was non inferior to enoxaparin 40 mg daily and has a similar safety profile. The studies which had been used in this analysis were the RE-NOVATE, RE-MODEL and RE-MOBILIZE trials, the same trials which the manufacturer used in the meta-analysis for its submission. The updated literature search also identified a pooled analysis (Friedman et al. 2010) which also analysed the same three trials. The authors of the pooled analysis also concluded that oral dabigatran was as effective as subcutaneous enoxaparin in reducing the risk of major VTE and VTE-related mortality after hip or knee arthroplasty and has a similar bleeding profile. The results of these publications are consistent with recommendation in TA157. The updated literature search did not identify any publications comparing dabigatran etexilate with fondaparinux.

The updated literature search identified five ongoing and one completed study which compared dabigatran etexilate with enoxaparin. Two of the ongoing studies (NCT01139658 [expected date of completion June 2012] and NCT00846807 [expected date of completion July 2011]) appear to address the Committee's research question regarding pragmatic trials of dabigatran etexilate. The results of the completed trial (RE-NOVATE II, (Eriksson 2010)) concluded that oral dabigatran was as effective and safe as subcutaneous enoxaparin after hip or knee arthroplasty and dabigatran had a similar bleeding profile. The up-dated literature search did not identify any trials comparing dabigatran etexilate with fondaparinux.

The Institute has published a number of pieces of relevant work relating to the prevention of venous thromboembolism. Rivaroxaban is recommended for the prevention of venous thromboembolism after total hip or total knee replacement in adults (TA170). There is also clinical guideline 92 'Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery' published in January 2010 (which effectively incorporated the recommendations of TA157) and VTE prevention quality standard which was published in June 2010. There is also an ongoing appraisal for apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery.

8. Implementation

A submission from Implementation is included in Appendix 3.

The publication of technology appraisal 157 does not appear to have a considerable effect on the pattern of prescribing for dabigatran etexilate in primary care. However, for this indication it is anticipated that most prescribing would take place in hospitals (inpatient and discharge medication). Table 1 in Appendix 3 indicates that hospital prescribing grew by 1,398% in 2009.

9. Equality issues

None

10. GE paper sign off: Janet Robertson, 26th May 2011

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review. The recommendations have been effectively incorporated into a clinical guideline (CG92). The guidance will remain on the static list until CG92 is reviewed.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)
ii. The technology falls within the scope of a clinical guideline (or public health guidance)
iii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
iv. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
v. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
    - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
    - There is evidence of unjustified variation across the country in access to a treatment
    - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
    - The treatment is excluded from the Payment by Results tariff

vi. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital CG92 Published: January 2010, Review: January 2013. Status: Replaces CG46.

Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. CG46. Published: April 2007. Status: Replaced by CG92.

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults TA170 Published: April 2009, Review: February 2012

VTE prevention quality standard. Published: June 2010.

In progress

Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery. Technology Appraisal. Referred: January 2010. Expected publication date: April 2012.

Suspended/terminated

Ximelagatran for the treatment of venous thromboembolism. Referred: October 2000. Status: removed from the work programme in December 2006. The manufacturer withdrew regulatory applications following receipt of trial data.

Venous thromboembolism (recurrent) - idraparinux sodium. Referred: November 2005. Status: Removed from the work programme in July 2007 when the manufacturer confirmed that the regulatory strategy was not finalised.

In topic selection[2]

[redacted]

[2] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

[redacted]

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
2.1 Dabigatran etexilate holds a marketing authorisation for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or elective total knee replacement surgery. Dabigatran is taken orally. 2.2 The summary of product characteristics (SPC) states that dabigatran etexilate treatment should be started within 1–4 hours of surgery with a half dose of 110 mg. Thereafter, treatment is continued with a standard dose of 220 mg once daily for 10 days after knee replacement and for 28–35 days after hip replacement. The SPC states that for special patient populations (including people with moderate renal impairment, those over 75 years and people receiving amiodarone), a reduced dose of 150 mg (75 mg starting dose, 150 mg continuing dose) once daily is recommended. Source: TA157.	No current changes. Source: BNF61 (March 2011) [redacted] Source: Letter from Boehringer Ingelheim, 21 March 2011 Proposed licence extensions are at various stages of the NICE STA process: Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation. Referred: July 2009. Expected date of publication: December 2011. Dabigatran etexilate for the treatment of acute venous thromboembolic events. Referred: July 2009. Status: The appraisal will begin once regulatory approval timelines are established. [redacted]

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Apixaban (Pfizer)	EU positive opinion recommending granting of a marketing authorisation for apixaban in preventing VTE in

Drug (manufacturer)	Details (phase of development, expected launch date,)
	adults undergoing hip or knee replacement, March 2011. [redacted] NICE Technology Appraisal expected publication: April 2012.
Darexaban (Astellas)	Venous thromboembolism (VTE) prevention following major orthopaedic surgery. In phase III clinical trials [redacted]
Edoxaban (Daiichi Sankyo)	Venous thromboembolism prophylaxis In phase III clinical trials [redacted]
Betrixaban (Portola Pharmaceuticals)	Venous thromboembolism (VTE) prevention In phase II clinical trials [redacted]
Oral heparin (Emisphere)	Venous thromboembolism (VTE) prevention In phase III clinical trials [redacted]

Registered and unpublished trials

Trial name and registration number	Details
Pradaxa (Dabigatran Etexilate) VTE Prevention After Elective Total Hip or Knee Replacement Surgery NCT01153698	An open, prospective, observational study to collect data on safety (major bleeding events) and efficacy (symptomatic venous thromboembolism (VTE)) of a switch from Enoxaparin to dabigatran etexilate in patients with total knee replacement (TKR) and total hip replacement (THR). Status: recruiting Participants: 375 Expected completion date: July 2011
An Open Label, Non-comparative, Pharmacokinetic and Pharmacodynamic Study to Evaluate the Effect of Pradaxa (Dabigatran Etexilate) on Coagulation Parameters Including a Calibrated Thrombin Time Test in Patients With Moderate Renal Impairment (Creatinine Clearance 30-50 ml/Min) Undergoing Elective Total Knee Replacement Surgery NCT01184989	Status: recruiting Participants: 100 Expected completion date: November 2011
Observational Cohort Study to Evaluate Safety and Efficacy of Pradaxa (Dabigatran Etexilate) in Patients With Moderate Renal Impairment (Creatinine Clearance 30-50 ml/Min) Undergoing Elective Total Hip Replacement Surgery or Total Knee Replacement Surgery NCT00847301	Status: recruiting Participants: 500 Expected completion date: April 2012
Observational cohort study on the prevention of venous thromboembolic events after elective orthopaedic surgery for Total Knee Replacement or Total Hip Replacement in patients treated with PRADAXA to evaluate the efficacy and safety of Pradaxa in real-life conditions NCT01139658	Status: recruiting Participants: 1600 Expected completion date: July 2012

Trial name and registration number	Details
Observational Cohort Study to Evaluate the Safety and Efficacy of Pradaxa (Dabigatran Etexilate) for the Prevention of Venous Thromboembolism in Patients Undergoing Elective Total Hip Replacement Surgery or Total Knee Replacement Surgery in a Routine Clinical Setting. NCT00846807	Status: recruiting Participants: 5190 Expected completion date: June 2011

Additional information

Safety

The FDA alerted the public on 30 March 2011 to storage and handling requirements for dabigatran (Pradaxa) capsules, due to the potential for product breakdown from moisture and loss of potency.
Source: FDA

Reference List

Dahl OE, Quinlan DJ, Bergqvist D et al. (2010) A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *Journal of Thrombosis and Haemostasis.* 8 (9): 1966-1975.

Eriksson BI (2010) Primary prevention of VTE after hip or knee arthroplasty - Experience with dabigatran etexilate. *Pathophysiology of Haemostasis and Thrombosis.* Conference: 21st International Congress on Thrombosis - The Start of a New Era Antithrombotic Agents Milan Italy. Conference Start: 20100706 Conference End: 20100709. Conference: 21st International Congress on Thrombosis - The Start of a New Era Antithrombotic Agents Milan Italy. Conference Start: 20100706 Conference End: 20100709. Conference Publication: (var.pagings): 117-.

Friedman RJ, Dahl OE, Rosencher N et al. (2010) Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: A pooled analysis of three trials. *Thrombosis Research.* 126 (3): 175-182.

Wolowacz SE, Roskell NS, Plumb JM et al. (2009) Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty: A meta-analysis. *Thrombosis and Haemostasis.* 101 (1): 77-85.

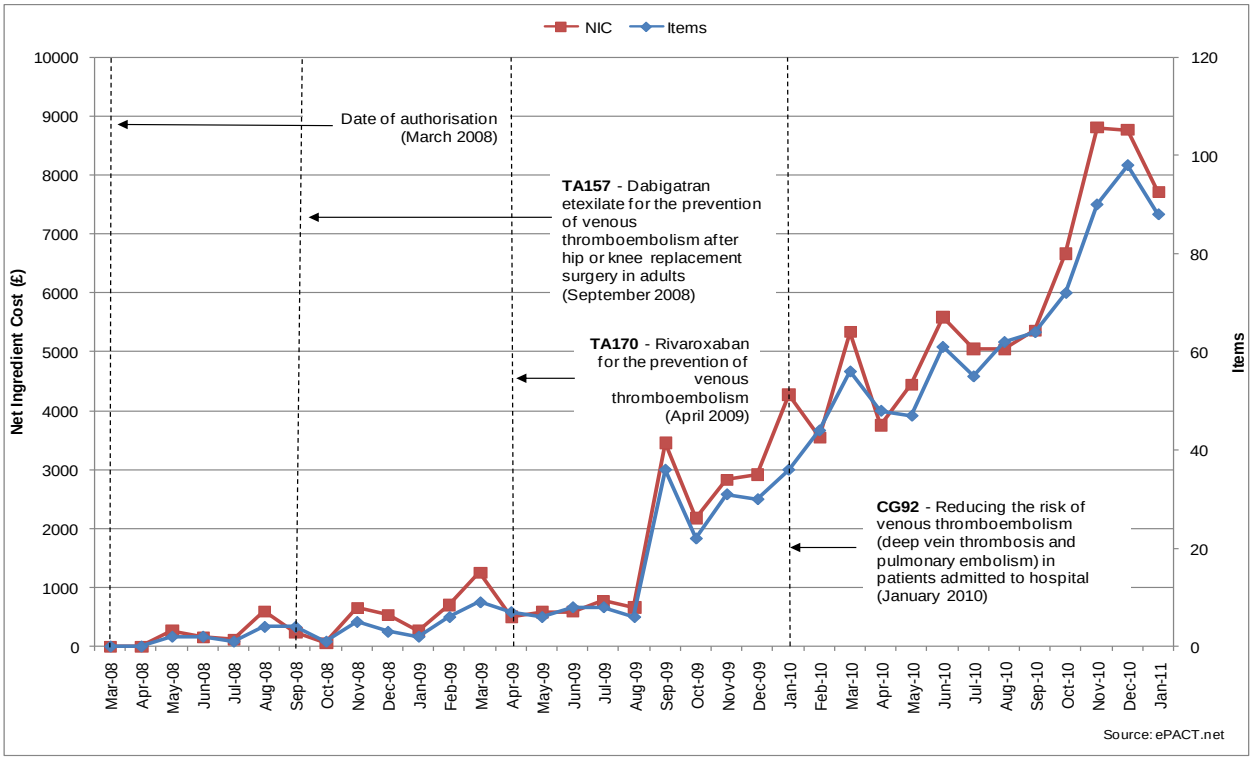
Appendix 3 – Implementation submission

1. Routine healthcare activity data

This section provides information on cost and volume for dabigatran etexilate (pradaxa) prescribed and dispensed in primary care in England using data obtained from the electronic Prescribing Analysis and Cost Tool (ePACT) system. All costs stated in this report are based on Net Ingredient Cost (NIC).

1.1 Primary care prescribing (ePACT) - dabigatran etexilate (pradaxa)

Figure 1 Trend in the cost and volume of prescribing dabigatran etexilate (pradaxa) in primary care in England



The above chart shows that the prescribing costs and volume for dabigatran etexilate (pradaxa) has increased over time. The publication of technology appraisal 157 does not appear to have a considerable effect on the pattern of prescribing for dabigatran etexilate. Prescribing data for January 2011 shows a fall in both prescribing cost and volume. It is unclear yet whether this is a temporary or ongoing trend.

This data does not link to diagnosis or age and the volume of prescribing is small, so needs to be treated cautiously in relation to the specific recommendations of the guidance.

Notes:

- The electronic prescribing analysis and cost tool (ePACT) system covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Pricing Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.
- Volume: The basic measure of volume in PACT data is the number of prescription items which refer to a single item on a prescription form.
- Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.
- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of items, although it does not account for patients receiving different dosages or durations.
- Unfortunately this data does not link to diagnosis or age so needs to be treated cautiously in relation to the specific recommendations of the guidance.

1.2 Hospital Prescribing, England: 2009

The Information Centre for Health and Social Care - Hospital Prescribing, England: 2009 (Available from: http://www.ic.nhs.uk/webfiles/publications/007_Primary_Care/hospre09/Hospital_Prescribing_2009.pdf)

Table 1.Estimated costs (£000s) for Dabigatran etexilate

Medicine	Hospital 2009	% growth	Primary care 2009	% growth	FP10HP 2009	% growth	Total 2009	% growth
Dabigatran etexilate*	563.2	1,398.0	16.7	536.1	0.3	-	580.3	1,342.4

*Approved by NICE in September 2008

2. External literature – Uptake Database (ERNIE) website.

There are currently no relevant publications on the Uptake Database (ERNIE).