NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA170; Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults

This guidance was issued in April 2009.

The review date for this guidance is February 2012.

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 rivaroxaban within its licensed indication for the prevention of venous thromboembolism after elective orthopaedic surgery of the lower limbs

3. Current guidance

1.1 Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery.

4. Rationale[1]

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 TA170 verbatim, the recommendation has been effectively incorporated in that rivaroxaban is included in the list of options for pharmacological VTE prophylaxis after surgery in both elective hip and elective knee replacement. The related technology appraisal, TA157 on dabigatran etexilate for the same indication has been incorporated into the guideline in the same way and was moved to the static list in August 2011.

There is no new evidence to suggest that the recommendations of TA170 should change nor any ongoing trials of rivaroxaban that might be expected lead to a change in the recommendations. There has been no relevant change to the price of rivaroxaban (it is now cheaper than it was at the time TA170 was developed).

[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

Based on this information, it is proposed that the guidance is placed on the static list until a decision is made to update CG92. Moving TA170 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 updated, then a new proposal for TA170 (and the related guidance TA157) can be developed during the pre-scoping stages of that guideline.

5. Implications for other guidance producing programmes

The Clinical Guidelines team at NICE agrees with the proposal and has no further comments to make.

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 November 2007 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 publication of TA170, the manufacturer of rivaroxaban applied for two licence extensions. In September 2011, the Committee for Medicinal Products for Human Use adopted two new positive opinions for these proposed licence extensions for rivaroxaban. One is for the prevention of stroke and systemic embolism in adult patients with non‑valvular, atrial fibrillation with one or more risk factors (such as congestive heart failure, hypertension, age greater than 75 years, diabetes mellitus, prior stroke or transient ischaemic attack). The other is for the treatment of deep vein thrombosis, and prevention of recurrent deep vein thrombosis and pulmonary embolism following an acute deep vein thrombosis in adults. These are the subject of two ongoing technology appraisals.

The price for rivaroxaban has decreased slightly since TA170 was published. Rivaroxaban currently costs £44.15 for a pack of ten 10 mg tablets (previously £45.00), £132.44 for 30 tablets (previously £135.00) and £441.45 for 100 tablets (excluding VAT, MIMS January 2012).

The updated literature search identified three ongoing studies and one study which has not yet open for recruitment. The first identified ongoing trial (NCT01478282 [expected completion June 2012]) is a Spanish safety study which aims to determine the effect of rivaroxaban and dabigatran on platelets and coagulation mechanisms under flow conditions. There are two ongoing, observational prospective studies: one which aims to study the safety and effectiveness of rivaroxaban in comparison with other pharmacologic agents (including low molecular weight heparin, fondaparinux, and vitamin K antagonists) in the prophylaxis of venous thromboembolism in a large sample of patients who undergo elective total hip replacement or total knee replacement in the real-life conditions as required by Korean Food and Drug Administration (NCT00831714 [expected completion November 2012]); and a post-

marketing pharmacovigilance surveillance study (NCT01029743 [expected completion March 2015]). The study which has yet to open for recruitment (last updated in September 2010) aims to compare the safety of dabigatran and rivaroxaban with low molecular weight heparin in the prevention of venous thromboembolism after knee arthroplasty surgery. (NCT01431456, [expected completion date October 2014]).

It is unlikely that the studies identified and slight change in price is likely to lead to a change in the recommendations of the original guidance.

The manufacturer of dabigatran etexilate has received a licence extension for the treatment of acute venous thromboembolic events. This topic is currently in the technology appraisals programme work stream. Dabigatran etexilate was originally recommended in TA157 and CG92 as an option within its marketing authorisation for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

Clinical guideline 92, “Venous thromboembolism: reducing the risk” was issued in January 2010 and will be reviewed in January 2013.

8. Implementation

A submission from Implementation is included in Appendix 3.

The implementation advice suggests that rivaroxaban increased in use after TA170 was published as expected.

9. Equality issues

During the development of the original guidance, the Committee discussed whether a recommendation for an oral treatment rather than a subcutaneous injection would give rise to any issues related to equalities and diversity legislation. However, the Committee concluded that there were no issues related to equality of access to treatment that it would need to take into account when considering positively recommending rivaroxaban. Consequently, no equality issues were raised in the original guidance.

GE paper sign off: Janet Robertson; Associate Director, Technology Appraisals – 2 February 2012

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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, as there is insufficient new evidence to have a material effect on our current guidance.
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No, as there is insufficient trial activity to anticipate a material effect on our current guidance.
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 appropriate technology appraisal review has been identified.
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 appropriate technology appraisal that has recent been referred to NICE has been identified.
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.	The only relevant clinical guideline, Management of venous thromboembolic diseases, has explicitly excluded prophylaxis against venous thromboembolism in the scope.

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).	The only relevant clinical guideline, Management of venous thromboembolic diseases, has explicitly excluded prophylaxis against venous thromboembolism in the scope.
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.	Yes. We did not identify relevant trial activity for this technology/indication to suggest a review date, or any significant trial activity to enable a comparison between rivaroxaban and other technologies for this indication.

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. 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

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. 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

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

Appendix 2 – supporting information

Relevant Institute work

Published

CG92 Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Published January 2010, with a review decision date of January 2013. It includes guidance from TA170 by suggesting rivaroxaban as an option 'in line with TA170...' in elective orthopaedic surgery for hip or knee. CG92 updates and replaces CG46 Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery.

TA157 Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. Published September 2008. Review decision August 2011 – transfer to the static list.

In progress

Management of venous thromboembolic diseases. CG in progress, expected June 2012. The scope excludes prophylaxis against venous thromboembolism.

Rivaroxaban for the treatment and secondary prevention of venous thromboembolism. Expected date of issue: July 2012.

Rivaroxaban for acute coronary syndrome. Expected date of issue: TBC.

Rivaroxaban for atrial fibrillation (stroke prevention). Expected date of issue: May 2012.

Dabigatran etexilate for the treatment and secondary prevention of recurrent symptomatic venous thromboembolism. Expected date of issue: TBC.

Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery. Expected date of issue: January 2012. The final appraisal determination document went out to consultation until 9 December 2011 and says "Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective hip or knee replacement surgery."

Paused

Rivaroxaban for the prevention of venous thromboembolism in people hospitalised for acute medical conditions. Referral date May 2011. As of August 2011, the expected date of issue is TBA.

The NeLM reported in April 2011: "According to results from the Phase III MAGELLAN study presented at the American College of Cardiology Annual Scientific Session, rivaroxaban is non-inferior to enoxaparin in short-term use and superior to it in long-term use in the prevention of venous thromboembolism (VTE) in hospitalised patients with acute medical illnesses, but at the expense of an increase in the rate of major and clinically relevant non-major bleeding.... According to a Reuters

Health report, the company will conduct additional analyses to see if rivaroxaban can be used more selectively in patients hospitalised with acute medical illness."

In topic selection[2]

[redacted]

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Rivaroxaban has a marketing authorisation for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.	As well as being in development for acute coronary syndrome and for stroke prevention in atrial fibrillation, there is a NICE appraisal in progress for rivaroxaban for the treatment and secondary prevention of venous thromboembolism. See above for details.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Apixaban (Bristol-Myers Squibb-Pfizer) for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery	A NICE technology appraisal is underway, and the expected date of issue is January 2012.

[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.

Registered and unpublished trials

Trial name and registration number	Details
Evaluation of the Potential Action of Coagulation Factors Concentrates in the Reversal of the Antithrombotic Action of New Oral Anticoagulants: Studies ex Vivo in Blood Samples From Healthy Volunteers NCT01478282	Phase IV safety study, not yet open for recruitment. Estimated enrollment: 10. Estimated study completion date: June 2012.
Xarelto in the Prophylaxis of Post Surgical Venous Thromboembolism After Elective Major Orthopedic Surgery of Hip or Knee (XAMOS) NCT00831714	Observational prospective study, currently recruiting. Estimated enrollment: 15000 Estimated study completion date: November 2012.
Xarelto® Regulatory Post-Marketing Surveillance NCT01029743	Observational prospective study, currently recruiting. Estimated enrollment: 4000 Estimated study completion date: March 2015.
A Randomized Pilot Study Comparing the Safety of DAbigatran and RIvaroxaban Versus NAdroparin in the Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery (DARINA) NCT01431456	Randomised phase III safety study, not yet open for recruitment. Estimated enrollment: 150 Estimated study completion date: October 2014.

Appendix 3 – Implementation submission

Implementation feedback: review of NICE technology appraisal guidance 170

NICE Technology Appraisal 170 Venous thromboembolism - rivaroxaban
Implementation input required by 12/11/2011
Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

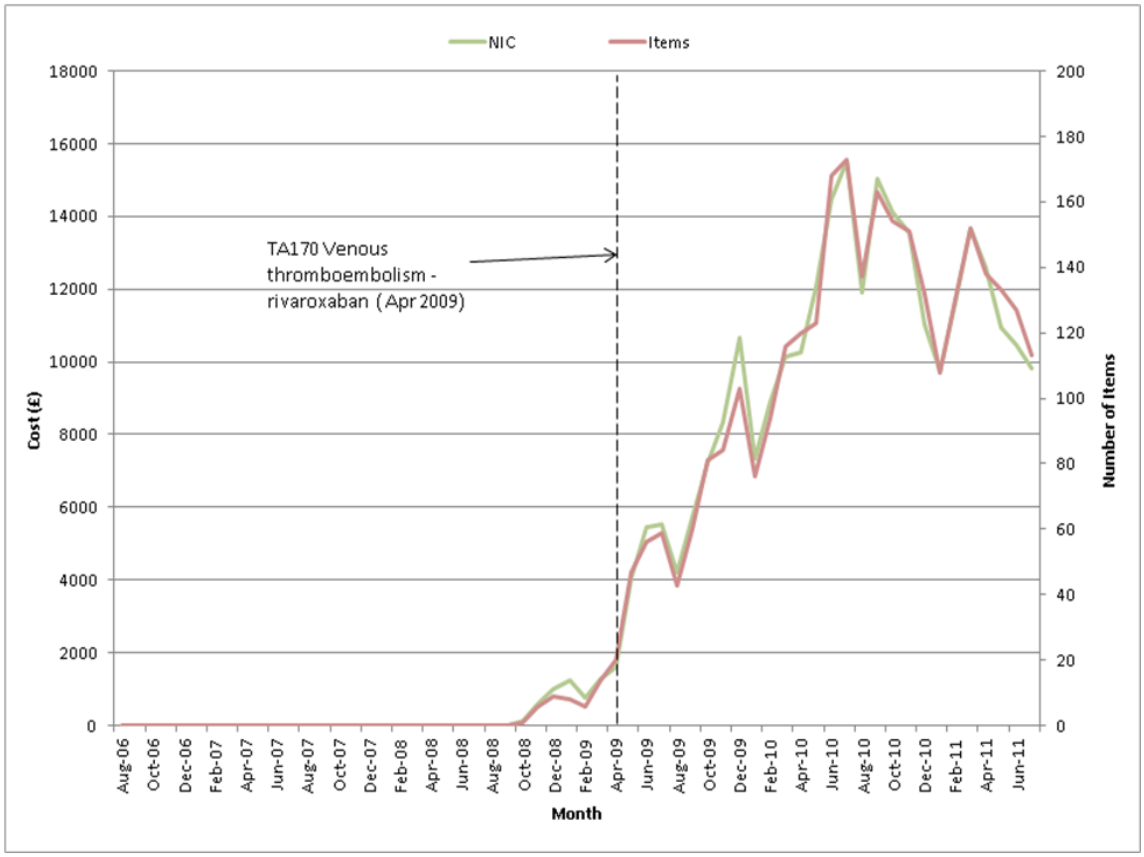
Contents

1 Routine healthcare activity data

1.1 ePACT data

This section provides ePACT data on the number of prescription items and the net ingredient cost (NIC) of rivaroxaban prescribed in primary and secondary care and dispensed in the community between August 2006 and July 2011.

Figure 1 The net ingredient cost (£) and the number of prescriptions items for rivaroxaban between August 2006 and July 2011.



2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

Nothing to add at this time.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Two comments have been received about this TA since 2009. One organisation commented that their Trust had been taking part in an audit of post-operative infections, and after a significant decline in their rates, had noticed an increase when this drug was introduced. They are not certain of the cause and effect, but they appear to be seeing a slightly higher wound leakage rate in orthopaedic patients. The evidence is, as yet, unpublished, but they have notified the MHRA and NPSA of their concerns. Another person commented (in 2009) that prophylaxis for VTE remained a contentious issue within their Trust, despite the TA and hoped that the forthcoming clinical guideline on VTE would help resolve this issue.

Appendix A: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services 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.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

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.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.