NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA261; Rivaroxaban for the treatment and secondary prevention of venous thromboembolism, and TA287; Rivaroxaban for the treatment of acute symptomatic pulmonary embolism with or without symptomatic DVT and the prevention of recurrent VTE

This guidance was issued in July 2012 (TA261) and June 2013 (TA287).

The review date for this guidance is May 2015 (TA261 and TA287).

1. Recommendation

TA261 and TA287 should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA261: To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment and secondary prevention of venous thromboembolism.

TA287: To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis and the prevention of recurrent venous thromboembolism.

3. Current guidance

TA261:

1.1 Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults

TA287:

1.1 Rivaroxaban is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

4. Rationale[1]

[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

No new evidence has been identified that suggests that a review of the guidance is necessary.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal. Existing guidance on venous thromboembolism prevention (CG92) and management (CG144) cross refer to these TAs. Discrete parts of both of these guidelines are currently being updated through the standing committee process however the areas being updated do not relate to the use of rivaroxaban.

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 April 2010 (TA261) and January 2012 (TA287) 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

The marketing authorisation for rivaroxaban at the time of developing technology appraisal 261 was for 'treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults'. The marketing for rivaroxaban at the time of developing technology appraisal 287 was for the 'treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults'. The company have indicated that it intends to [redacted] and [redacted].

Since the development of technology appraisals 261 and 287 dabigatran etexilate received a marketing authorisation, in April 2014, for the 'treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults' and could therefore be a comparator for rivaroxaban for both indications in NICE technology appraisals 261 and 287.

The literature searches identified 12 relevant references, since the development of NICE technology appraisals 261 and 287, 9 of these observed venous thromboembolism (Arachchillage et al., 2015, Coleman et al 2014, Gomez-Outes et al., 2014, Kakkos et al 2014, Prins et al., 2013, Rollins et al., 2014, van der Hulle et al., 2014, van et al., 2014 and Vedovati et al., 2015), 2 for deep vein thrombosis (Bamber et al., 2013 and Wasserlauf et al., 2013) and 1 for pulmonary embolism (Prins et al., 2015).

The Committees for technology appraisal 261 and 287 noted there was no direct trial evidence demonstrating that rivaroxaban is superior to a LMWH in patients with cancer. In the evidence search, 1 study carried out a systematic review and meta-

analysis of randomised controlled trials observing the treatment of cancer-associated recurrent venous thromboembolism (Vedovati et al., 2015). The study compared oral anticoagulant therapies including dabigatran (n=2 studies), rivaroxaban (n=2 studies), edoxaban (n=1 study) and apixaban (n=1 study) with conventional anticoagulation treatment but details of these conventional treatments were unavailable. The study concluded that oral anticoagulant therapies were as effective as standard treatment and perhaps safer but this evidence is not enough to allow a review of this question.

The Committee for technology appraisal 287 noted that the maximum length of treatment in EINSTEIN-PE was 12 months, but some people will need longer treatment durations in clinical practice. However, the Committee accepted that there was no biological or pharmacological reason why the effects of rivaroxaban would not be maintained over the long term. The 1 pulmonary embolism reference, Prins et al., 2015, was a patient satisfaction survey comparing rivaroxaban with enoxaparin or a vitamin K antagonist and therefore cannot answer this question from the Committee.

There have been no changes to the acquisition costs of rivaroxaban or the comparators.

The clinical effectiveness evidence identified from the literature searches, registered trials and current list prices of the technologies do not suggest the recommendations of technology appraisal 261 and 287 need reviewing.

Based on the above information, it is proposed that technology appraisal guidance 261 and 287 are transferred to the 'static guidance list'.

8. Implementation

A submission from Implementation is included in Appendix 3.

The ePACT data suggests that there was an increase in the cost and volume of rivaroxaban prescribed and dispensed in the community and hospitals, after technology appraisals 261 and 287 were published.Equality issues

During consultation on the scope for technology appraisal 261 it was suggested that due consideration should be given to people who on religious or cultural values object to receiving pig-derived heparin. The range of available products in this therapeutic area means that it was not considered that this needs to be addressed by the Committee.

During consultation on the scope for technology appraisal 287 1 of the consultees commented "Separate consideration of those patients unable to take warfarin". During the scoping process it was determined that this was not an equalities issue as patients unable to take warfarin are not a protected group. The comment was presented to the Committee for information but was not discussed further.

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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. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
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
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	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. The review will be conducted through the MTA process.	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.	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. 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

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (2015) NICE technology appraisal 335.

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation (2013) NICE technology appraisal 275. *Incorporated into CG36 along with TA249 and TA256 and moved to the static list. NB CG36 has been updated and replaced by CG180 Atrial fibrillation (2014).*

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (2012) NICE technology appraisal 249.

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (2012) NICE technology appraisal 256.

Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (2012) NICE technology appraisal 245.

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement in adults (2008) NICE technology appraisal 157. *Review decision August 2011: transfer to the static list.*

Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (2014) NICE technology appraisal 327.

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (2009) NICE technology appraisal 170. *Review decision May 2012: transfer to the static list.*

Venous thromboembolism: reducing the risk in patients admitted to hospital (2010) NICE guideline CG92. *Review decision July 2014: standard update, in progress, publication expected June 2015. NB no new evidence was put forward, but stakeholders felt there was sufficient variation in practice to warrant a review.*

Venous thromboembolic diseases (2012) NICE guideline CG144. *Review decision August 2014: to update via standing committee, in progress, publication expected November 2015.*

In progress

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal guidance. Publication expected June 2015.

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. NICE technology appraisal guidance. Publication expected October 2015.

Referred - QSs and CGs

Acute medical admissions in the first 48 hours – referred QS.

Consultant review within 12 hours of admission – referred QS.

Perioperative care – referred QS.

Readmissions – referred QS.

Urgent and emergency care – referred QS.

Suspended/terminated

Vorapaxar for reducing atherothrombotic events after a myocardial infarction or in peripheral vascular disease. NICE technology appraisal guidance. Publication date to be confirmed. *19 December 2014: "Please note that following on from information received from the company, this appraisal will be rescheduled to align with the commercial availability of the product within the UK."*

Rivaroxaban for the prevention of venous thromboembolism in people hospitalised for acute medical conditions. NICE technology appraisal guidance. Publication date to be confirmed. *8 June 2012: "The Institute has now been informed by the manufacturer that it is not currently pursuing a licensing application for rivaroxaban in this indication."*

[redacted]

Venous thromboembolism (recurrent) - idraparinux sodium. NICE technology appraisal guidance. Publication date to be confirmed.
23 July 2007: "The manufacturer of idraparinux sodium has advised us that the regulatory strategy in relation to this product is not finalised. The Institute has therefore decided to remove this appraisal from its work programme."

Apixaban for the prevention of venous thromboembolism in acute medical illness. NICE technology appraisal guidance. Publication date to be confirmed.
20 March 2014: "The Institute has now been informed by the manufacturer that it will no longer be pursuing a licensing application for apixaban in this indication, therefore, NICE has decided to suspend this appraisal on its current work programme."

Ximelagatran for the treatment of venous thromboembolism (terminated appraisal) (2006) NICE technology appraisal guidance.

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
TA261: "Rivaroxaban (Xarelto, Bayer) is indicated for the 'treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults'. For the initial treatment of acute deep vein thrombosis, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrence. The duration of treatment recommended in the summary of product characteristics depends on bleeding risk and other clinical criteria: short-term treatment (3 months) is recommended for those with transient risk factors such as recent surgery and trauma, and longer treatment for permanent risk factors or idiopathic (unprovoked) deep vein thrombosis. The summary of product characteristics further states that experience with rivaroxaban in this indication for more than 12 months is limited. A reduced dosage of 15 mg twice daily for 21 days followed by 15 mg once daily should be used in people with moderate (creatinine clearance 30–49 ml/min) or severe (creatinine clearance 15–29 ml/min) renal impairment. Rivaroxaban costs £2.10 per 15 mg or 20 mg tablet. The cost of treatment is estimated to be £235.86, £427.61 and £811.13 for 3, 6 and 12 months of treatment respectively." TA287: "Rivaroxaban (Xarelto, Bayer) is indicated for the 'treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults'. For the initial treatment of acute pulmonary embolism, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrent venous thromboembolism."	The cost and indication are the same (eMC last updated December 2014; eBNF February 2015)

Registered and unpublished trials

Trial name and registration number	Details
Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk. (MARINER) NCT02111564 CR103834, 2014-000305-13, RIVAROXDVT3002	Phase III, randomised double blind trial. Status: currently recruiting. Estimated enrolment: 8000. Primary completion date: February 2017.
Influence of Rivaroxaban Compared to Vitamin K Antagonist Treatment Upon Development of Cardiovascular Calcification in Patients With Atrial Fibrillation and/ or Pulmonary Embolism. NCT02066662 12-001	Phase IV, randomised open label trial. Status: currently recruiting. Estimated enrolment: 253. Primary completion date: January 2016.
Prospective, Multicenter Study Investigating Efficacy and Safety of Oral Rivaroxaban for the Prevention of Recurrent Venous Thromboembolism in Korean Patients With Cancers. NCT01989845 KVTE13-01	Phase IV, open label single group assignment trial. Status: currently recruiting. Estimated enrolment: 127. Primary completion date: August 2016.
Reduced-dosed Rivaroxaban and Standard-dosed Rivaroxaban Versus ASA in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis and/or Pulmonary Embolism. (EinsteinChoice) NCT02064439 16416	Phase III, randomised double blind trial. Status: currently recruiting. Estimated enrolment: 2850. Primary completion date: November 2016.

Trial name and registration number	Details
The VICTORIA Study (Vascular CalcIfiCation and sTiffness Induced by ORal antIcoAgulation) Comparison Anti-vitamin K Versus Anti-Xa. (VICTORIA) NCT02161965 2012-005354-27	Phase IV, randomised single blind trial. Status: currently recruiting. Estimated enrolment: 150. Primary completion date: May 2016.
FIRST Registry: Follow-up in Rivaroxaban Patients in the Setting of Thromboembolism UKCRN ID 17766	Observational cohort study. Current status: open. Closure date: 01/11/2017. Global sample size 1500.
Rivaroxaban Observational Safety Evaluation (ROSE) Study UKCRN ID 13911	'Observational post-authorisation safety specialist cohort event monitoring study.' Current status: open. Closure date: 18/02/2017. Global sample size 3400.
Xarelto® for Long-term and Initial Anticoagulation in Venous Thromboembolism (VTE) (XALIA) NCT01619007	Observational study: "The main goal is to analyze long-term safety in the use of rivaroxaban in the treatment of acute DVT in routine clinical practice." Status: Ongoing, not recruiting. Estimated enrolment: 5172. Primary completion date: March 2015.

References

Arachchillage DR, Efthymiou M, Mackie IJ et al. (Feb. 2015) Rivaroxaban and warfarin achieve effective anticoagulation, as assessed by inhibition of TG and in-vivo markers of coagulation activation, in patients with venous thromboembolism. *Thrombosis Research* 135 (2): 388-393.

Bamber L, Wang MY, Prins MH et al. (Oct. 2013) Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. *Thrombosis & Haemostasis* 110 (4): 732-741.

Coleman CI, Limone BL, Bookhart BK et al. (May 2014) Cost-effectiveness analysis of extended duration anticoagulation with rivaroxaban to prevent recurrent venous thromboembolism. *Thrombosis Research* 133 (5): 743-749.

Gomez-Outes A, Terleira-Fernandez AI, Lecumberri R et al. (Oct. 2014) Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. *Thrombosis Research* 134 (4): 774-782.

Kakkos SK, Kirkilesis GI, Tsolakis IA (Nov. 2014) Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *European Journal of Vascular & Endovascular Surgery* 48 (5): 565-575.

Prins MH, Lensing AW, Bauersachs R et al. (2013) Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thrombosis Journal [Electronic Resource]* 11 (1): 21-.

Prins MH, Bamber L, Cano SJ et al. (Feb. 2015) Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of pulmonary embolism; results from the EINSTEIN PE trial. *Thrombosis Research* 135 (2): 281-288

Rollins BM, Silva MA, Donovan JL et al. (Oct. 2014) Evaluation of oral anticoagulants for the extended treatment of venous thromboembolism using a mixed-treatment comparison, meta-analytic approach. *Clinical Therapeutics* 36 (10): 1454-1464

Van der Hulle T, Kooiman J, den Exter PL et al. (2014) Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. [Review]. *Journal of Thrombosis & Haemostasis* 12 (3): 320-328

Van EN, Coppens M, Schulman S et al. (Sept. 2014) Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 124 (12): 1968-1975

Vedovati MC, Germini F, Agnelli G et al. (Feb. 2015) Direct Oral Anticoagulants in Patients With VTE and Cancer: A Systematic Review and Meta-analysis. *Chest* 147 (2): 475-483.

Wasserlauf G, Grandi SM, Filion KB et al. (Aug. 2013) Meta-analysis of rivaroxaban and bleeding risk. *American Journal of Cardiology* 112 (3): 454-460

Appendix 3 – Implementation submission

1. Routine healthcare activity data

ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of rivaroxaban prescribed in hospitals and or the community and dispensed in the community in England.

Chart 1 - Cost and volume of rivaroxaban prescribed in hospitals and dispensed in the community in England between April 2010 and September 2014

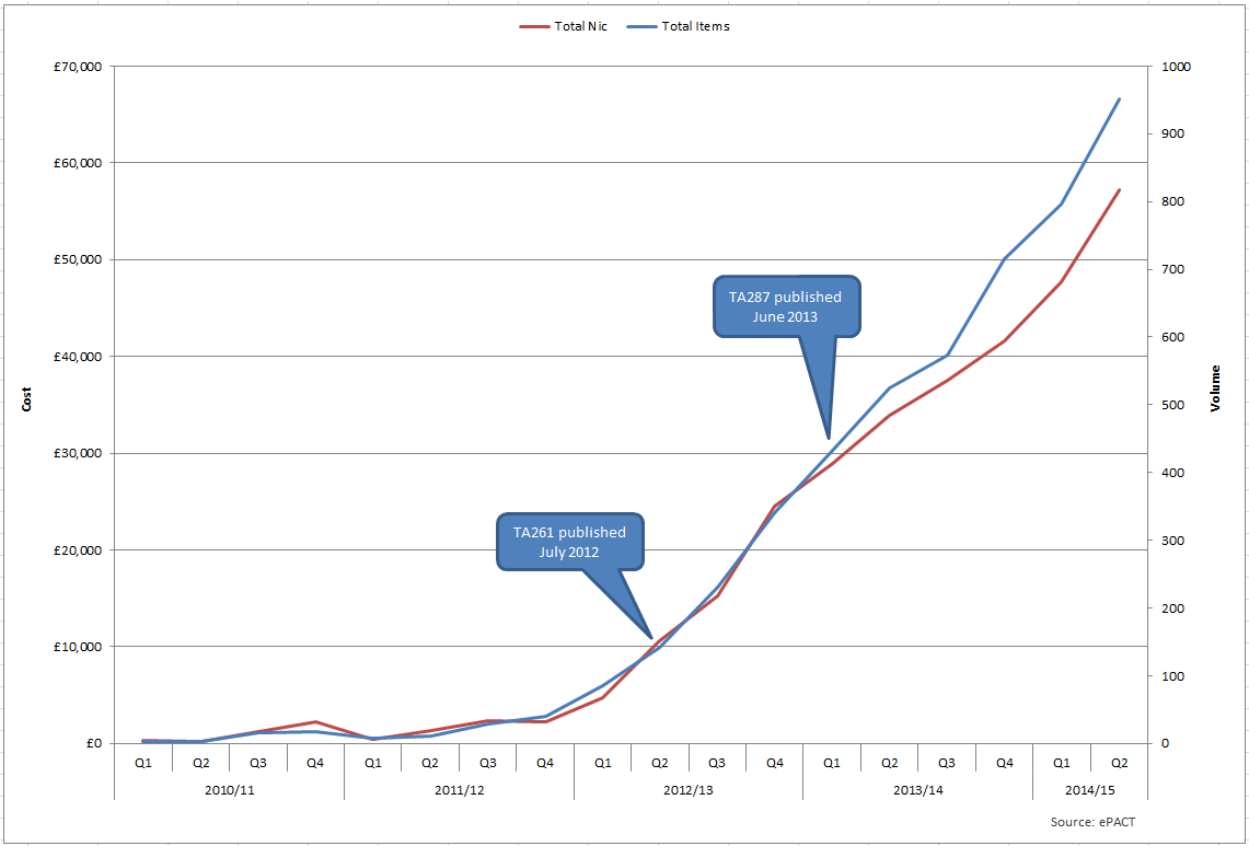
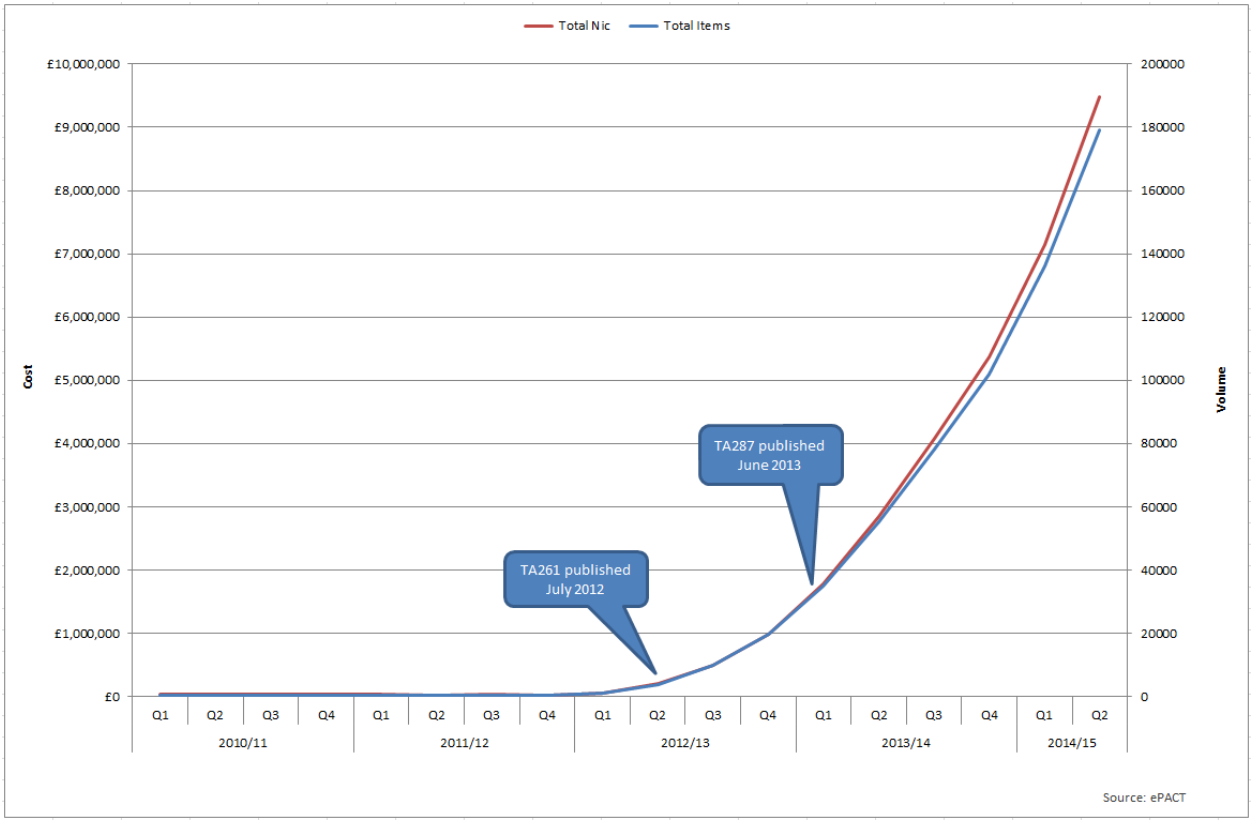


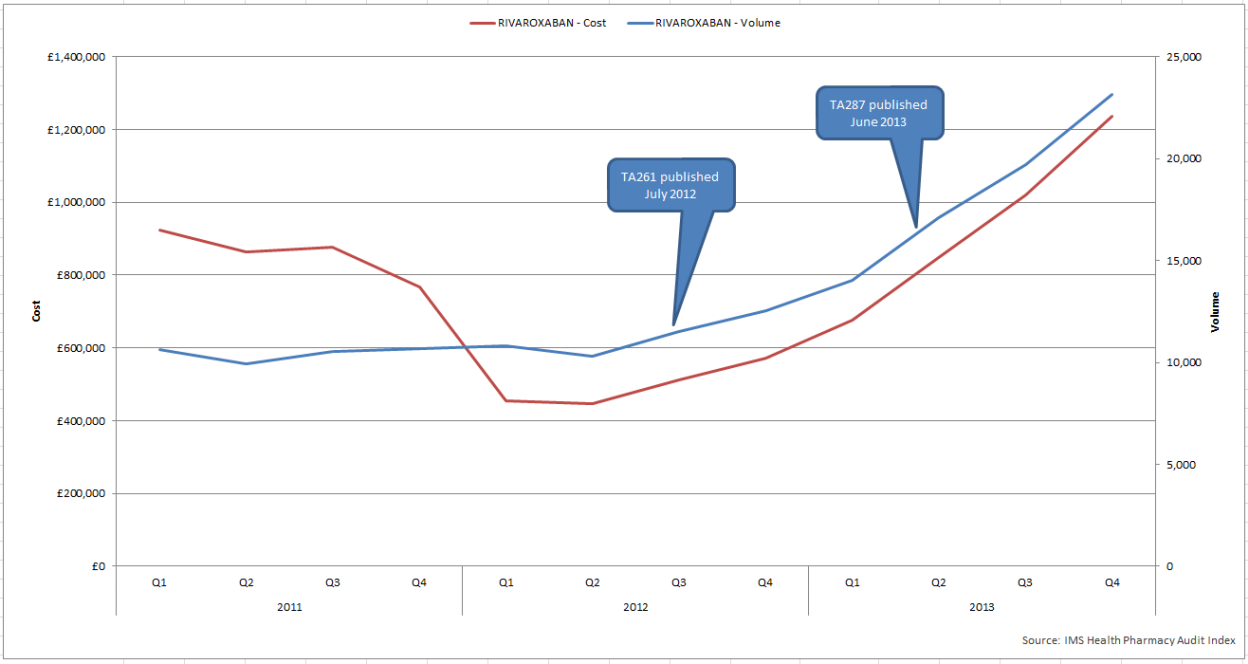
Chart 2 - Cost and volume of rivaroxaban prescribed and dispensed in the community in England between April 2010 and September 2014



Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of rivaroxaban prescribed and dispensed in hospitals in England between January 2012 and January 2013.

Chart 3 - Cost and volume of rivaroxaban prescribed in hospitals in England between January 2001 and December 2013.



2. Implementation studies from published literature

No uptake information was found for TA261 or TA287.

3. Qualitative input from the field team

The implementation field team recorded the following feedback in relation to TA261 and TA287.

Subject	Notes	Owner	Created On
Technology appraisals	Commissioners are taking an increased interest in compliance with NICE technology appraisals in advance of the publication of the balanced scorecard. Proposing to introduce a uniform, and quite detailed, monitoring system for all providers in the county. Oral anticoagulants:- some debate about how best to introduce these drugs into the Trust without increasing complexity and potential risk. Have divided usage into three broad categories although these are not exclusive: dabigatran - atrial fibrillation rivaroxaban - deep vein thrombosis/stroke prevention apixoban - hip and knee surgery.	Chris Connell	17/12/2012
Technology appraisals	Venous thromboembolism - rivaroxaban: Prophylaxis for VTE remains a vexed area within the trust - looking forward to this TAG and the forthcoming CG to help resolve this issue.	Chris Connell	16/04/2009

4. Implementation studies from shared learning

A search of the shared learning website highlighted no examples of TA261 or TA287 being implemented.

Appendix A: Healthcare activity data definitions

ePACT

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 dispensed in hospitals, 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.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.
Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.
Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.

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