Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

apixaban 2.5mg film-coated tablet (Eliquis®) SMC No. (741/11)

Bristol-Myers Squibb Pharmaceuticals Ltd/Pfizer Ltd.

04 November 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

apixaban (Eliquis®) is accepted for use within NHS Scotland.

Indication under review: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

In two large phase III double-blind comparative studies, in patients undergoing elective hip or knee replacement surgery, apixaban was superior to a low molecular weight heparin for the incidence of VTE and all cause death whilst incidence of major bleeding events was similar between groups.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 December 2011

Indication

Prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery.

Dosing Information

Apixaban 2.5mg taken orally, twice daily. The initial dose should be taken 12 to 24 hours after surgery. In patients undergoing hip replacement surgery the recommended duration of treatment is 32 to 38 days and for knee replacement surgery the recommended duration of treatment is 10 to 14 days.

Product availability date

September 2011

Summary of evidence on comparative efficacy

Apixaban inhibits free factor Xa (FXa) as well as thrombus-associated FXa and FXa within the prothrombinase complex. Unlike the indirect inhibitors of FXa, apixaban does not require antithrombin III to inhibit FXa. By inhibiting FXa, apixaban reduces directly tissue factor-induced thrombin generation and indirectly thrombin-mediated platelet aggregation.

Two similarly designed double-blind multi-centre, randomised phase III studies have been conducted comparing oral apixaban with subcutaneous enoxaparin for the prevention of venous thromboembolism (VTE). ADVANCE 2 was conducted in patients undergoing elective unilateral or same day bilateral total knee replacement (TKR) surgery or revision and ADVANCE 3 in patients undergoing elective unilateral total hip replacement (THR) surgery or revision.[1,2] Patients were randomised to apixaban 2.5mg orally twice daily (first dose given 12 to 24 hours after wound closure) or enoxaparin 40mg subcutaneous injection once daily (first injection given 12 hours before surgery). Study treatments continued for 10 to 14 days in ADVANCE 2, and 32 to 38 days in ADVANCE 3, at which point bilateral venography was performed. The primary efficacy analysis was conducted in all patients randomly assigned to treatment who had an assessable efficacy outcome (i.e. had a venogram adjudicated as assessable, developed confirmed deep vein thrombosis [DVT] or pulmonary embolism [PE] or who died from any cause).

In ADVANCE 2, non-inferiority of apixaban to enoxaparin was tested first using a pre-specified non-inferiority margin (an upper limit of the 95% confidence interval (CI) of the relative risk (RR) of ≤1.25, and for the absolute risk difference an upper limit of the 95% CI of ≤5.6%), for the primary efficacy endpoint. If both these criteria were met then superiority of apixaban over enoxaparin was tested. In ADVANCE 3, non-inferiority of apixaban to enoxaparin for the primary efficacy endpoint was tested first using the same pre-specified non-inferiority margin upper limit of the 95% CI. If non-inferiority was established for the primary efficacy endpoint, the secondary efficacy outcome was tested for non-inferiority using a pre-specified non-inferiority margin upper limit of the 95% CI of the RR of ≤1.5. If apixaban met these non-inferiority criteria, superiority of apixaban over enoxaparin was tested using Pearson's Chi-square test.

In both studies, the primary endpoint was composite and included all adjudicated asymptomatic or symptomatic DVT, non-fatal PE or death from any cause during the intended treatment

period. Secondary endpoints included major venous thromboembolism (VTE) defined as adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE or VTE-related death during the intended treatment period. In ADVANCE 2, the number of patients randomised to the apixaban group was 1528 and to enoxaparin was 1529 and the primary efficacy analysis was performed in 64% (976/1528) and 65% (997/1529) of patients respectively. In ADVANCE 3 the number of patients randomised to the apixaban group was 2708 and to enoxaparin was 2699 and the primary efficacy analysis was performed in 72% (1949/2708) and 71% (1917/2699) of patients respectively. Apixaban was superior to enoxaparin for the primary endpoint and the secondary endpoint of major VTE in both studies (see table below).

Table: Primary endpoint and key secondary endpoint for ADVANCE 2 and ADVANCE 3 [1, 2]

Endpoints	**Apixaban % (n/N)**	**Enoxaparin % (n/N)**	**Relative risk (95% CI)**	**Absolute risk difference (95% CI)**
ADVANCE 2				
Primary endpoint: VTE and all cause death	15% (147/976)	24% (243/997)	0.62 (0.51 to 0.74)	-9.3% (-12.7 to -5.8)
Secondary endpoint: major venous thromboembolism	1.1% (13/1195)	2.2% (26/1199)	0.50 (0.26 to 0.97)	-1.0% (-2.0 to -0.05)
ADVANCE 3				
Primary endpoint: VTE and all cause death	1.4% (27/1949)	3.9% (74/1917)	0.36 (0.22 to 0.54)	-2.5% (-3.5 to -1.5)
Secondary endpoint: major venous thromboembolism	0.5% (10/2199)	1.1% (25/2195)	0.40 (0.15 to 0.80)	-0.7% (-1.3 to -0.2)

CI= confidence interval

In ADVANCE 2 there were four (one fatal) versus no PE and in ADVANCE 3 three (one fatal) versus five (all non-fatal) PE in the apixaban and enoxaparin groups respectively.

Summary of evidence on comparative safety

The primary safety endpoint in both studies was bleeding during the treatment period and was categorised as major, clinically relevant non-major or minor and as the composite of major/clinically relevant non-major. There was no significant difference between the rates of major bleeding events between the groups. In ADVANCE 2 0.6% (9/1501) versus 0.9% (14/1508) of patients had adjudicated major bleeding events in the apixaban and enoxaparin groups respectively (absolute risk difference -0.33%, 95% CI -0.95 to 0.29). In ADVANCE 3 major bleeding events were observed in 0.8% (22/2673) versus 0.7% (18/2659) of patients in the apixaban and enoxaparin groups respectively (absolute risk difference 0.1%, 95% CI -0.3 to 0.6). Furthermore, there were no significant differences between treatment groups for clinically relevant non-major bleeding events and for the composite of major or clinically relevant non-major bleeding events. The European Medicines Agency (EMA) considered that the bleeding

profile of apixaban in THR and TKR was acceptable and considered its safety profile to be comparable to enoxaparin.[3]

Elevations in hepatic transaminase (>3x upper limit of normal [ULN]) and bilirubin (>2x ULN) levels were infrequent in both groups. Overall across both studies (in the treatment and follow-up period) thrombocytopenia occurred in four patients in the apixaban group versus six patients in the enoxaparin group and there were three versus five cases of stroke.

Summary of clinical effectiveness issues

Apixaban was shown to be superior to subcutaneous enoxaparin 40mg daily for the primary endpoint of adjudicated VTE and all cause death in two studies of patients undergoing knee or hip replacement surgery. In both studies the results of the clinically significant major VTE endpoint were mainly driven by the favourable results of proximal DVT; nine versus 26 cases in ADVANCE 2 and seven versus 20 cases in ADVANCE 3, for the apixaban and enoxaparin groups respectively. In both studies a major bleeding event occurred in less than 1% of patients and there were no significant differences between treatment groups. However, the higher rate of PE in the apixaban group in the ADVANCE 2 study remains unexplained.

In the pivotal studies the mean age of patients was 61 to 66 years, <2% had a history of DVT and <1% a history of PE, and mean weight was around 80kg. Factors such as age, obesity and previous history of VTE are known to increase the risk of VTE. The number of patients included in the two pivotal studies with these risk factors was limited. These patient populations are reflective of most clinical studies in this therapeutic area but may not truly represent those treated in clinical practice.

There are no direct data comparing apixaban to the other oral anticoagulants dabigatran and rivaroxaban. The submitting company presented an adjusted indirect comparison using Bucher methodology in order to compare apixaban, dabigatran and rivaroxaban using enoxaparin as a common comparator. The indirect comparison has limitations which include that measures of heterogeneity were not reported and inconsistencies between measures of outcomes in the studies. Results for knee and hip populations indicate that dabigatran was significantly less efficacious than apixaban for the composite of all VTE and all-cause death. However there was no significant difference for the apixaban versus rivaroxaban comparison. For bleeding endpoints apixaban, dabigatran and rivaroxaban had similar outcomes. The statistician consulted by SMC considered the results of the indirect comparison to show that there was no significant difference in terms of efficacy between apixaban and rivaroxaban. A mixed treatment comparison (MTC) was also provided by the submitting company and its methodology was considered to be more robust. Results of the MTC indicate that apixaban is similar to dabigatran and rivaroxaban.

Apixaban (along with dabigatran and rivaroxaban) offers the advantage over low molecular weight heparin (LMWH) of an oral preparation which does not require regular monitoring and dose adjustment or daily subcutaneous injections. When prophylaxis is continued for up to 5 weeks, this may be an advantage in the community setting. However, apixaban is administered twice daily compared to once daily administration for rivaroxaban and dabigatran.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing apixaban to enoxaparin, rivaroxaban, and dabigatran. The analysis was based on two linked economic models: a decision tree which covered the period up to 90 days from the operation (TKR and THR modelled separately) and a Markov model extending the results over 35 years. The key efficacy variables were the composite of "all deaths plus all VTEs" and bleeding. Rates for the different medicines compared were taken from an indirect comparison using the Bucher method, although a mixed treatment comparison was also performed but was utilised in sensitivity analysis rather than in the base case. The consequences of these events were modelled and were assumed to be independent of the initial medicine prescribed once an event had occurred.

Utility values were attached to events such as DVT, pulmonary embolism and intracranial haemorrhage. These were based on a search of the research literature and seemed reasonable.

Resource use included medicines costs and administration, and management of adverse events. The costs of VTE events were also included and covered events such as DVT, pulmonary embolism and intracranial haemorrhage. The number of events was predicted by the economic models and costs were attached from UK sources, which seemed appropriate. The results, which included an amendment to reflect a change in the price of dabigatran, were as follows:

TKR	**Quality adjusted life years (QALYs)**	**Cost**		**Difference in QALYs**	**Difference in Cost**	**Conclusion**
Apixaban	8.5581	£355.80				
Rivaroxaban	8.5724	£328.77		-0.0143	£27.03	Rivaroxaban dominant
Dabigatran	8.5133	£493.97		0.0448	-£138.17	Apixaban dominant
Enoxaparin	8.5088	£626.50		0.0493	-£270.70	Apixaban dominant
THR						
Apixaban	8.9954	£196.31				
Rivaroxaban	8.9967	£225.86		-0.0013	-£29.55	£22,731/QALY vs apixaban
Dabigatran	8.9839	£208.90		0.0115	-£12.59	Apixaban dominant
Enoxaparin	8.9814	£434.41		0.014	-£238.10	Apixaban dominant

The submission reports for TKR

- apixaban, rivaroxaban and dabigatran dominated enoxaparin
- rivaroxaban dominated both apixaban and dabigatran
- apixaban dominated dabigatran.

For THR

- apixaban, rivaroxaban and dabigatran dominated enoxaparin
- apixaban dominated dabigatran
- rivaroxaban has a cost per QALY of £22,731 versus apixaban

One-way and probabilistic sensitivity analyses were carried out. The findings were robust to a variety of changes in assumptions, the main difference being in terms of the ICER against rivaroxaban in THR.

Potential weaknesses with these findings are that the results are based on point estimates of differences in effectiveness and failure to take account of the statistical significance of the results. In addition, they are based on the adjusted (Bucher) indirect comparison provided and SMC's statistical advisor suggested that the MTC was the more robust type of analysis.

The MTC suggests there are no statistically significant differences between apixaban, rivaroxaban and dabigatran, and if this is accepted then the comparison is on the basis of medicine acquisition costs. Apixaban has a cost that is similar to or cheaper than rivaroxaban, depending on the duration of treatment. Dabigatran is cheaper, but SMC clinical expert advice suggests it is not widely used in Scotland and hence is not the most relevant comparator.

Despite these weaknesses the committee concluded that the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Anticoagulant Europe.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 122; Prevention and management of venous thromboembolism in December 2010. The guideline makes the following recommendations for prophylaxis following orthopaedic surgery:

- Patients undergoing total hip replacement or total knee replacement surgery should receive pharmacological prophylaxis (with low molecular weight heparin (LMWH), fondaparinux, rivaroxaban or dabigatran) combined with mechanical prophylaxis unless contraindicated.
- Extended prophylaxis should be given.

The National Institute for Health and Clinical Excellence (NICE) published guideline 92; Venous thromboembolism: reducing the risk [Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital] in January 2010.
The guideline includes the following recommendations:

- Base the choice of pharmacological VTE agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.
- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery or elective knee replacement surgery.
    - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of: dabigatran etexilate (starting 1 to 4 hours after surgery); fondaparinux sodium (starting 6 hours after surgical closure provided haemostasis has been established); LMWH (starting 6 to 12 hours after surgery);

rivaroxaban (starting 6 to 10 hours after surgery); unfractionated heparin (for patients with renal failure) (starting 6 to 12 hours after surgery).

- Continue pharmacological VTE prophylaxis for 28 to 35 days (for hip replacement surgery and 10 to 14 days (for knee replacement surgery), according to the summary of product characteristics for the individual agent being used.

The guidelines predate the licensing of apixaban.

Additional information: comparators

SIGN guidance recommends LMWH, fondaparinux, rivaroxaban or dabigatran combined with mechanical prophylaxis unless contraindicated for prophylaxis following orthopaedic surgery.

Cost of relevant comparators

Drug	Dose Regimen	Knee		Hip	
		Duration (days)	Cost (£)	Duration (days)	Cost (£)
Apixaban	**2.5mg orally twice daily**	**10 to 14**	**34 to 48**	**32 to 38**	**110 to 130**
Fondaparinux	2.5mg subcutaneously 6 hours after surgery then once daily	5 to 9	38 to 63	33	213
Rivaroxaban	10mg orally once daily	14	61	35	154
Dalteparin	5000IU subcutaneously evening before surgery then once daily	5 to 7	17 to 23	35	102
Dabigatran	110mg orally on day one then 220mg once daily thereafter	10	24	28 to 35	69 to 87
Drug	**Dose Regimen**	**Duration (days)**			**Cost (£)**
Enoxaparin	40mg subcutaneously 12 hours before surgery then once daily	7 to 10*			32 to 44
Tinzaparin	4500IU subcutaneously 12 hours before surgery then once daily	7 to 10*			29 to 39
Bemiparin	3,500 IU subcutaneously 2 hours before or 6 hours after surgery then once daily	7 to 10*			22 to 30

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 August 2011 with exception of apixaban (cost from company's submission) and bemiparin (cost from BNF March 2011).

*The SPCs for enoxaparin, tinzaparin and bemiparin do not state specific treatment durations following knee and hip surgery, therefore a cost for 7 to 10 days treatment is given. However SIGN 122 (December 2010) includes a general recommendation (in relation to orthopaedic surgery) that extended prophylaxis should be given.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 14,304 in year 1 and 14,554 in year 5. Based on an estimated uptake of 2% in year 1 and 3.15% in year 5, the impact on the medicines budget was estimated at £23K in year 1 (£6K for TKR, £17K for THR) and £36K in year 5 (£9K for TKR, £27K for THR). Market share was assumed to be taken from all existing treatments. The net medicines budget impact was estimated as a saving of £8K in year 1 (saving of £3k for TKR and £5K for THR) and a £12K saving in year 5 (saving of £5K for TKR and £7K for THR).

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

1. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807-15.

2. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Eng J Med 2010;363:2487-2498.

3. European Medicines Agency. European Public Assessment Report for apixiban (Eliquis®). EMEA/H/C/002148.

This assessment is based on data submitted by the applicant company up to and including 17 October 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.