Scottish Medicines Consortium

dabigatran etexilate, 75mg and 110mg hard capsules (Pradaxa®)
No. (466/08)

Boehringer Ingelheim Ltd

09 May 2008

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

dabigatran etexilate (Pradaxa®) is accepted for use within NHS Scotland for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

In two large phase lll studies, in patients undergoing either total knee or total hip replacement surgery, dabigatran was non-inferior to low molecular weight heparin in the incidence of VTE and all cause mortality with patients having a similar incidence of major bleeding events. The two drugs have similar costs per dose but dabigatran has lower administration costs and is an oral therapy. This may facilitate longer duration of thromboprophylaxis, however the risks and benefits of this longer treatment duration need to be considered on a case-by-case basis.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing information

220mg orally once daily. Treatment should be initiated with 110mg within 1 to 4 hours of elective surgery, continuing with 220mg once daily thereafter for a total of 10 days for knee replacement surgery and 28 to 35 days for elective hip replacement surgery.

If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 220mg once daily.

A lower daily dose of 150mg is recommended in the elderly (>75 years) and patients with moderate renal impairment. A 75mg capsule is available to facilitate treatment in these patient groups.

Product availability date

04 April 2008

Summary of evidence on comparative efficacy

Dabigatran etexilate is a prodrug hydrolysed in the plasma and liver to the active dabigatran. It is an oral, competitive, reversible, direct thrombin inhibitor which inhibits free and fibrin-bound thrombin and thrombin-induced platelet aggregation.

There are two pivotal, randomised, double-blind, phase lll studies of similar design, one in patients undergoing total knee replacement (TKR) and one in patients undergoing total hip replacement (THR), which support this primary prevention licence indication. The objective of the studies was to prove the non-inferiority of dabigatran to enoxaparin.

Of the 5595 patients randomised to either dabigatran or enoxaparin, 5539 adult patients went on to undergo primary TKR surgery (n=2076) or primary THR surgery (n=3463) and be treated with either dabigatran (75 or 110mg within 1 to 4 hours of completion of surgery, provided there was good haemostasis, then 150 or 220mg once daily thereafter) or enoxaparin (40mg subcutaneously daily, beginning the evening before surgery) for 6 to 10 days for TKR surgery and 28 to 35 days for THR. Concomitant treatment with low dose aspirin and selective cyclo-oxygenase-2 inhibitors was allowed during treatment. Elastic compression stockings were permitted.

The primary outcome was a composite endpoint of the incidence of total venous thromboembolic events (VTE - defined as venographic or symptomatic deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE)) and all-cause mortality during the treatment period. Secondary efficacy endpoints included a composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality, proximal DVT, total DVT, symptomatic DVT, symptomatic PE and death during the treatment period. Bilateral venographic assessment was undertaken within 24 hours of the last oral dose and patients were followed up for three months. The non-inferiority margin was derived to demonstrate preservation of at least two-thirds of the 95% confidence interval difference between enoxaparin and placebo and was set at 9.2% for the TKR study and 7.7% for the THR study. Sample size

calculations assumed that 25% of patients would have a non-evaluable venogram in the TKR study and 35% in the THR study. The primary analysis set included all patients randomised, who received at least one dose of medication, had surgery and had confirmed VTE data during the treatment period.

Both doses of dabigatran were shown to be non-inferior to enoxaparin for the primary efficacy outcome in both the TKR and THR studies. (Table 1). In both studies the main component of the primary outcome was asymptomatic DVTs.

Table 1. Primary efficacy outcomes for the Total Knee Replacement study and the Total Hip Replacement study

	Dabigatran 220mg	**Dabigatran 150mg**	**Enoxaparin 40mg**
Total Knee Replacement study			
Primary analysis set (n)	503	526	503
Total VTE and all-cause mortality % (95% CI)	36.4 (32.2 to 40.6)	40.5 (36.3 to 44.7)	37.7 (33.5 to 41.9)
Risk difference versus enoxaparin % (95% CI)	-1.3 (-7.3 to 4.6)*	2.8 (-3.1 to 8.7)*	
Total Hip Replacement study			
Primary analysis set (n)	880	874	897
Total VTE and all-cause mortality % (95% CI)	6.0 (4.5 to 7.6)	8.6 (6.7 to 10.4)	6.7 (5.1 to 8.3)
Risk difference versus enoxaparin % (95% CI))	-0.7 (-2.9 to 1.6)**	1.9 (-0.6 to 4.4)**	

CI = confidence interval; *Within the pre-defined non-inferiority margin of 9.2% ** Within the pre-defined non-inferiority margin of 7.7 %.

The secondary outcome of major VTE and VTE-related mortality occurred in 2.6% and 3.8% of dabigatran 220mg and 150mg patients compared with 3.5% of enoxaparin patients in the TKR study and 3.1% and 4.3% of dabigatran 220mg and 150mg patients compared with 3.9% of enoxaparin patients in the THR study.

Summary of evidence on comparative safety

The primary safety outcome was the occurrence of bleeding events during study treatment (major bleeding events, clinically relevant non-major bleeding events and minor bleeding events). An experienced and independent committee of experts, blinded to all treatment allocations, adjudicated all bleeding events centrally using pre-defined and detailed rules.

There was no significant difference in bleeding events between either dose of dabigatran and enoxaparin. Most major bleeding events were at the surgical wound site (89% in the TKR study and 91% in the THR study). There were no fatal bleeding events in the TKR study and two in the THR study (one in each of the dabigatran groups).

The incidence of hepatotoxicity and cardiac events was low in both studies and comparable to enoxaparin. The most common reason for treatment discontinuation was gastrointestinal disorders in the THR study and cardiac events in the TKR study.

Summary of clinical effectiveness issues

In two large phase lll studies, dabigatran was comparable to enoxaparin in the incidence of VTE and all cause mortality in patients undergoing either total knee or total hip replacement surgery with patients having a similar incidence of bleeding events. Factors such as age > 75 years, extremities of weight, renal insufficiency and previous VTE are known to increase both the risk of VTE and bleeding. The number of patients included in the two pivotal studies with these risk factors was limited. This patient population is reflective of most clinical studies in this therapeutic area but it may not truly represent those treated in clinical practice.

The composite primary outcome was mainly driven by asymptomatic, venographically detected VTE. The incidences of clinically relevant symptomatic PE and mortality are too rare to be used as primary endpoints as the patient numbers required for such a study would be too large. However, there are a number of uncertainties in using these asymptomatic thrombi which may not go on to cause a clinical event. The incidence of major bleeding events, the primary safety outcome, is also very low and therefore although similar in both the above studies, it should be noted that to show a significant difference in such a rare event would require large patient numbers.

The drugs used and the length of treatment for thromboprophylaxis in orthopaedic surgery varies across Scotland with both aspirin and low molecular weight heparin (LMWH) being used along with compression stockings and mobilisation. This reflects the current Scottish Intercollegiate Guidelines Network (SIGN) recommendation. Since 2003, the Scottish Arthroplasty Project has monitored and reported on the outcomes of orthopaedic surgery. The median length of inpatient stay for both operations is 7-8 days with around one third of patients receiving thromboprophylaxis during their inpatient stay only and just over 50% continuing for up to six weeks for both TKR and THR. This study of outcomes of TKR and THR surgery has shown a steady decrease in the incidence of VTE and mortality.

Dabigatran offers the advantage of an oral preparation which does not require regular monitoring and dose adjustment or daily subcutaneous injections. When prophylaxis is continued for up 5 weeks this may be an advantage in the community setting.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing dabigatran to both LMWH and aspirin in patients after THR and TKR surgery. The methodology adopted a decision tree to model the acute phase (10 weeks post surgery) and used a Markov model for the chronic phase. Clinical data came from the two pivotal studies; the enoxaparin results were assumed to represent the efficacy and safety rates for all LMWHs. An indirect comparison was undertaken for aspirin.

Utility data, resource use and costs came from appropriate sources and were judged to be robust. Probability distributions were applied to the main parameters and the distributions used were appropriate. The main weakness was the assumption that in Scotland patients after a hip replacement receive LMWH for 30 days.

The base case results reported that dabigatran dominated LMWH and aspirin for both procedures. It had lower lifetime costs and a higher quality of life than the alternatives but the differences in costs and outcomes were extremely small. For example, in patients post hip replacement, the mean lifetime cost saving for dabigatran 220mg compared to LMWH was £93 and mean lifetime QALY gained were 0.01. The modelling showed dabigatran had a very high probability of being cost-effective at a threshold of £20,000 per QALY.

The results were sensitive to the clinical efficacy data and event rate. Adopting the clinical event rate observed in the hip replacement clinical study to predict symptomatic events resulted in dabigatran delivering slightly fewer QALYs (0.013), with an associated saving of £92. However dabigatran dominated the comparators using the pooled event rate data. Sensitivity analyses also showed dabigatran was cost-effective compared to administering LMWH for 7.6 days. Dabigatran was cost-effective compared to aspirin under all scenarios.

The economic submission was complex but transparent, well presented and all assumptions were clearly referenced. The robust sensitivity analyses support the conclusion that dabigatran is likely to be cost-effective compared to LMWH and aspirin.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

Patient Interest Group Submission: Anticoagulation Europe

Additional information: guidelines and protocols

In October 2002, SIGN published guideline number 62, Prophylaxis of venous thromboembolism. A consultation on a proposed review was published in 2005. The 2002 guideline recommends for consideration, mechanical prophyaxis, aspirin, unfractionated heparin, LMWH or warfarin.

In April 2007, the National Institute for Health and Clinical Excellence (NICE) published Clinical Guideline number 46, Venous thromboembolism: reducing the risk of venous thromoembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. This guideline recommends mechanical prophylaxis in combination with either LMWH or fondaparinux.

Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 8th November 2002 that fondaparinux is appropriate for use in NHS Scotland. Compared with enoxaparin, fondaparinux has been shown to be associated with fewer thromboembolic events and a generally similar incidence of major bleeding. It is licensed for post-operative initiation, and this represents an advantage where regional anaesthesia and/or catheterisation are planned. It is predicted to be a cost-effective alternative to enoxaparin in a robust economic model. It may be considered for patients for whom antithrombotic therapy is appropriate, recognising that other antithrombotic agents and other approaches to prophylaxis may be more suitable in some situations.

After review of a full re-submission the Scottish Medicines Consortium (SMC) issued advice on 9th July 2007 that bemiparin 3,500 IU / 0.2ml (Zibor) is not recommended for use within NHS Scotland for the prevention of thromboembolic events in patients undergoing orthopaedic surgery. Bemiparin was associated with a lower incidence of thromboembolic complications than unfractionated heparin and was non-inferior to another low molecular weight heparin. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Additional information: comparators

Vitamin K antagonists, aspirin, LMWH, fondaparinux, mechanical compression hosiery, foot pumps.

Cost of relevant comparators

Drug	Dose regimen	Cost per 10 days (£)	Cost per 28 to 35 days (£)
Dabigatran	**110mg orally on day 1 then 220mg once daily**	**40**	**116 to 145**
Fondaparinux	2.5mg sc daily	67	186 to 233
Enoxaparin	40mg sc daily	42	118 to 147
Tinzaparin	4500IU sc daily*	36	100 to 125
Dalteparin	5000IU sc daily	28	79 to 99
Warfarin	Orally as determined by prothrombin time	< 1	1 to 2
Aspirin	150mg orally once daily	< 1	< 1

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27th February 2008. * or according to body weight.

Additional information: budget impact

The manufacturer estimates that the expenditure on existing drug therapies will be £405,275 in year 1: with dabigatran this could rise to £419,800, an increase of £14,525. In year 5 baseline costs are forecast at £582,960, rising to £773,280 an increase of £190,320 with dabigatran. Resource savings from avoiding the administration costs of LMWH reduce the cost increase to £7,770 in year 1, rising to £101,340 in year 5.

These forecasts assume 5,886 patients receive a hip replacement and 5,672 a knee replacement in year 1. These are based on the Scottish Arthroplasty Project annual report 2007. Growth is assumed to be in line with growth in the population.

Dabigatran is assumed to have a market share of 3% in year 1 rising to 37% in year 5 and this seems plausible.

These figures assume that currently patients with a THR receive LMWH for 30 days. If one assumes these patients do not receive LMWH beyond 10 days but dabigatran would be prescribed for 30 days then the incremental costs of introducing dabigatran could rise substantially from the figures presented.

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.

This assessment is based on data submitted by the applicant company up to and including 23 April 2008.

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.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission.

Eriksson BI, Dahl OE, Rosencher N, et al. for the RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56

Eriksson BI, Dahl OE, Rosencher N, et al. for the RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5:2178-85.

Scottish Arthroplasty Project Annual Report 2007. NHS Scotland. Available at http://www.arthro.scot.nhs.uk/.