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

bivalirudin 250mg powder for concentrate for solution for injection or infusion (Angiox) SMC No. (638/10)

The Medicines Company

06 August 2010

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

bivalirudin (Angiox) is accepted for restricted use within NHS Scotland.

Indication under review: as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Bivalirudin should be administered with aspirin and clopidogrel.

Restriction: patients who would have been considered for treatment with heparin in combination with a glycoprotein IIb/IIIa inhibitor. It should not be used as an alternative to heparin alone.

In patients with STEMI undergoing PCI, bivalirudin, compared with heparin plus a glycoprotein IIb/IIIa inhibitor, was associated with significantly lower rates of major bleeding, cardiac death and thrombocytopenia.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Bivalirudin should be administered with aspirin and clopidogrel.

Dosing Information

0.75mg/kg bolus intravenous (iv) injection then 1.75mg/kg/hour iv infusion for at least the duration of the procedure and up to four hours after PCI if clinically warranted then, as clinically necessary, a 0.25mg/kg/hour iv infusion for 4 to 12 hours. Bivalirudin should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures.

Product availability date

20 November 2009

Summary of evidence on comparative efficacy

Bivalirudin is a direct thrombin inhibitor that has recently had an extension to its marketing authorisation to include use as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Its initial indication was for use as an anticoagulant in patients undergoing PCI, including percutaneous transluminal coronary angioplasty (PTCA) procedures like angioplasty and PTCA with stenting. The initial indication was supported by a pivotal study that excluded patients with PCI performed as reperfusion therapy for acute myocardial infarction. The licence extension allows use of bivalirudin in these patients and is supported by one pivotal study.

The pivotal single-blind phase III study randomised in a 1:1 ratio 3,602 patients with STEMI undergoing PCI to anticoagulation with (i) unfractionated heparin (60 IU/kg intravenous (iv) bolus with subsequent boluses titrated to achieve an activated clotting time (ACT) of 200 to 250 seconds) plus glycoprotein IIb/IIIa inhibitor (GPI) (abciximab 0.25mg/kg iv bolus then 0.125mcg/kg/min iv infusion for 12 hours or eptifibatide 180mcg/kg iv bolus then 2mcg/kg/min iv infusion for 12 to 18 hours, with a second iv bolus dose given 10 minutes after the first) or (ii) bivalirudin (0.75mg/kg iv bolus then 1.75mg/kg/hour iv infusion) with provisional GPI given only to patients with no reflow or giant thrombus after PCI. Heparin and bivalirudin were discontinued at the end of PCI, but could be continued at low doses if clinically indicated. Randomisation was stratified by pre-procedural heparin use (heparin vs. no heparin); thienopyridine loading dose (clopidogrel 300mg vs. 600mg vs. ticlopidine 500mg); GPI (abciximab vs. eptifibatide) and site (US vs. non-US). Following angiography patients with lesions eligible for stenting were randomised in a 3:1 ratio to stent implantation with paclitaxel-eluting stent (TAXUS®) or identical uncoated bare metal stent (EXPRESS®).

For the first randomisation, the primary endpoint was net adverse clinical events (NACE), defined as major bleeding or a composite of major adverse cardiovascular events (MACE), consisting of death, re-infarction, target vessel revascularisation for ischaemia or stroke at 30 days. Within the intention-to-treat (ITT) population, that included all randomised patients, there

were significantly fewer NACE in the bivalirudin group compared with the heparin/GPI group, 9.2% (166/1,800) vs. 12.1% (218/1,802), relative risk 0.76 (95% confidence interval (CI): 0.63 to 0.92). This was mainly due to a significantly reduced rate of major bleeding (the primary safety endpoint), 4.9% vs. 8.3%, in the respective groups, relative risk 0.60 (95% CI: 0.46 to 0.77). The rates of MACE (the other component of the primary outcome) were similar in both groups: 5.4% and 5.5%, respectively, relative risk 0.99 (95% CI: 0.76 to 1.30).

In the ITT population at 30 days there was a significantly reduced rate of death from cardiac causes in the bivalirudin group compared with the heparin/GPI group, 1.8% (32/1,800) vs. 2.9% (52/1,802), relative risk 0.62 (95% CI: 0.40 to 0.95), with a corresponding reduction in death from all causes, 2.1% vs. 3.1%, relative risk 0.66 (95% CI: 0.44 to 1.00).

Among the 3,124 patients in whom stents were successfully implanted, there was no significant difference between bivalirudin and heparin/GPI in the rates of stent thrombosis at 30 days: 2.5% (39/1,571) vs. 1.9% (30/1,553), respectively. In prespecified analyses, the stent thrombosis rate within the first 24 hours was significantly greater with bivalirudin compared with heparin/GPI, 1.3% vs. 0.3%. Between 24 hours and 30 days respective rates were 1.2% and 1.7%.

In prespecified analyses at one year in the ITT population Kaplan-Meier estimated event rate for NACE was significantly lower with bivalirudin compared with heparin/GPI, 15.6% (275/1,800) vs. 18.3% (325/1,802), which was mainly due to a lower rate of major bleeding, 5.8% vs. 9.2%, respectively. Rates of MACE were similar in the respective groups, 11.9% and 11.9%. Cardiac mortality was also significantly lower with bivalirudin compared with heparin/GPI, 2.1% vs. 3.8%, hazard ratio 0.57 (95% CI: 0.38 to 0.84), with a corresponding reduction in all-cause mortality, 3.5% vs. 4.8%, HR 0.71 (95% CI: 0.51 to 0.98). Stent thrombosis was similar between groups, 3.6% vs. 3.2%, HR 1.13 (95% CI: 0.77 to 1.65). Target lesion revascularisation for ischaemia was more frequent with bivalirudin, 6.0% vs. 4.5%, although not significant (p=0.051).

Summary of evidence on comparative safety

As noted previously, in the pivotal study the primary safety endpoint, major bleeding at 30 days, was significantly reduced in the bivalirudin group compared with the heparin/GPI group, 4.9% (89/1,800) vs. 8.3% (149/1,802), respectively, relative risk 0.60 (95% CI: 0.46 to 0.77). In patients with baseline platelets counts >150,000/mm^3, rates of thrombocytopenia were significantly lower in the respective bivalirudin group compared with the heparin/GPI group, with moderate thrombocytopenia (<100,000/mm^3) in 1.1% (19/1,665) and 2.9% (48/1,653); severe thrombocytopenia (<50,000/mm^3) in 0.3% and 0.9%; and profound thrombocytopenia (<20,000/mm^3) in 0% and 0.4%.

In the pivotal study within the respective bivalirudin and heparin/GPI groups there were similar rates of any adverse effect: 55% and 57%; serious adverse effects: 15% and 17%, and serious adverse effects leading to study discontinuation: 0.7% and 0.6%. However, in this open-label study the rate of adverse effects related to study drug was significantly lower with bivalirudin compared to heparin/GPI: 8.6% vs. 15%. There were also fewer serious adverse effects related to study drug in the bivalirudin group: 1.4% vs. 2.3%.

Summary of clinical effectiveness issues

The Scottish Coronary Revascularisation Register 2008/09 Annual Report notes that 73% of urgent or emergency coronary angiographies were performed via radial arterial approach. In the pivotal study only 5.9% of procedures were via radial arterial access, with the majority via femoral arterial approach. Radial access is associated with lower rates of major bleeding than femoral access. When access-site major bleeding is removed from analyses, bivalirudin remains associated with a significant reduction in major bleeding compared to heparin/GPI: 2.5% (45/1,800) vs. 4.4% (79/1,802), relative risk 0.57 (95% CI: 0.40 to 0.82), although the treatment effect was smaller. Therefore, in Scotland the reduction in major bleeding with bivalirudin compared with heparin/GPI may be less than that observed in the study.

Published reports of the pivotal study suggest that the reduction in cardiac mortality with bivalirudin, compared with heparin/GPI may be attributable to the reduction in major bleeding and thrombocytopenia. However, the European Medicines Agency considers the differential mortality rates are likely caused by differences in timing of stent thrombosis and consequent target vessel revascularisation. During the index hospital admission, stent thrombosis rates in the bivalirudin and heparin/GPI groups were 2.2% and 1.3%, respectively, and corresponding target vessel revascularisation rates were 2.2% and 1.4%. After discharge from hospital respective rates of stent thrombosis were 0.6% and 0.9%. Patients with stent thrombosis were more likely to undergo ischaemic target vessel revascularisation if treated with bivalirudin, 84% (36/43) vs. 62% (21/34). This was directly associated with the timing of the stent thrombosis events as 81% (35/43) in the bivalirudin group occurred during hospitalisation (median time of onset 1 day) compared with 59% (20/34) in the heparin/GPI group (median time of onset 7 days). Patients who had early stent thrombosis were more likely to be monitored, undergo target vessel revascularisation, and therefore survive than those experiencing later stent thromboses. It has been noted that GPIs have not been associated with a lower risk of stent thrombosis but rather a later onset. Patients who would otherwise be treated with heparin alone may not obtain the cardiac mortality benefits of bivalirudin observed in the study, which appear to result from less effective management of later stent thrombosis associated with GPIs.

In the pivotal study comparator group patients received the GPIs, eptifibatide or abciximab. However, in Scotland the majority of patients receive tirofiban. It is not possible to be certain that the difference in GPI use would not affect clinical effectiveness, however, the available evidence suggests that it should not be a significant concern.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis making the comparison between bivalirudin and heparin/GPI in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. The model used was a decision analysis with a Markov model. Costs and benefits were estimated over the lifetime of the patient. The pivotal study was the data source for clinical event variables. This was supplemented by data on resource use from UK sources and on utilities from an EQ-5D survey of UK patients who had survived a myocardial infarction.

In the base case, bivalirudin was claimed to dominate the heparin/GPI treatment option (a saving of £567 and quality adjusted life year (QALY) gain of 0.09 per patient). Sensitivity analysis suggested the main factors in determining these results were costs of bivalirudin, savings on GPI, and changes in PCI length-of-stay.

The main concern was with the generalisability of some aspects of the pivotal study such as the use of radial access for PCI and the GPI used (with tirofiban being the predominant option in Scotland). A sensitivity analysis was run with 100% of PCIs using radial access and 100% use of tirofiban (and no saving on PCI length-of-stay); this resulted in a cost per QALY of £5,069 for bivalirudin versus heparin/GPI. As such, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In February 2007 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 93 on acute coronary syndromes. This recommends that patients with an ST elevation acute coronary syndrome should be treated immediately with primary PCI. Also, patients undergoing primary PCI should be treated with a glycoprotein IIb/IIIa receptor antagonist and intracoronary stent implantation should be used. In relation to anticoagulant therapy, it notes that in the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with an acute coronary syndrome should be treated immediately with low molecular weight heparin or fondaparinux. Anticoagulant therapy should be continued for eight days or until hospital discharge or coronary revascularisation.

In 2008 the European Society of Cardiology (ESC) published guidelines on the management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. These recommend that reperfusion therapy is indicated for all patients with a history of chest pain/discomfort for <12 hours and with persistent ST-segment elevation or (presumed) new left bundle-branch block and that it should be considered if there is clinical and/or electrographic evidence of ongoing ischaemia even, if, according to the patient, symptoms started >12 hours before. Primary PCI (defined as an angioplasty and/or stenting without prior or concomitant fibrinolytic therapy) is the preferred treatment if performed by an experienced team as soon as possible after first medical contact. The results of the pivotal study of bivalirudin are summarised in the guidelines, however, no recommendation is made about a preferred anticoagulant for use in PCI. It is noted that heparin is standard anticoagulant therapy during PCI.

Additional information: comparators

Heparin and heparin plus GPI. The GPI, abciximab, is licensed for prevention of ischaemic cardiac complications in patients undergoing PCI. However, the other GPIs, eptifibatide and tirofiban, are used “off-label” for PCI.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Bivalirudin	0.75mg/kg iv bolus then 1.75mg/kg/hr iv infusion	**310**
Heparin plus abciximab	60iu/kg iv bolus then titrate to ACT 200 to 250s 0.25mg/kg iv bolus then 0.125mcg/kg/min iv infusion for 12hours	752
Heparin plus tirofiban**	60iu/kg iv bolus then titrate to ACT 200 to 250s 25mcg/kg iv bolus then 0.15mcg/kg/min iv infusion for 18-24 hours	294
Heparin plus eptifibatide*	60iu/kg iv bolus then titrate to ACT 200 to 250s 180mcg/kg iv bolus repeated after 10 minutes plus 2mcg/kg/min iv infusion for 12-18 hours	114
Heparin	100iu/kg iv bolus then titrate to ACT 250 to 350s	3

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 31 May 2010. The above dose regimens have assumed that heparin and bivalirudin are only continued for the duration of PCI (as recommended in ESC guidelines and pivotal study protocol), which is assumed to be one hour and patient weight is assumed to be 70kg.

* unlicensed indication for eptifibitide using dose from HORIZONS-AMI study

** unlicensed indication for tirofiban using dose from STRATEGY; MULTISTRATEGY and FATA studies

Additional information: budget impact

In the manufacturer's submission it was estimated that if all patients were switched to bivalirudin immediately the medicines budget saving would be £354k in year 1 rising to £626k in year 5. For a lower rate of switching (especially in year 1) the saving is reduced proportionately. Including the effects on treatments and hospital stay, it was estimated by the manufacturer that the saving would rise from £569k in year 1 and £1m in year 5. The number of eligible patients was estimated to be 856 in year 1 rising to 1,512 in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

Stone G, Witzenbichler B, Guagliumi G et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008; 358: 2218-30

Mehran R, Lansky A, Witzenbichler B et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009; 374: 1149-59

European Medicines Agency, Assessment report for Angiox procedure number EMEA/H/C/II/0024. Doc ref no EMEA/724835/2009. London, 20 November 2009

Mehran R, Brodie B, Cox DA et al. The harmonizing outcomes with revascularisatin and stents in acute myocardial infarction (HORIZONS-AMI) trial: study design and rationale. Am Heart J 2008; 156: 44-56

This assessment is based on data submitted by the applicant company up to and including 16 July 2010.

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.