

**bivalirudin, 250mg powder for concentrate for solution for injection
or infusion (Angiox®)**

No. (516/08)

The Medicines Company UK Ltd

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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 for the treatment of adult patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction) planned for urgent or early intervention. It is restricted to use in patients who would otherwise have been considered for heparin in combination with a glycoprotein IIb/IIIa antagonist. In these patients bivalirudin monotherapy may be a suitable alternative. It should not be used as an alternative to heparin alone.

Bivalirudin should be administered with aspirin and clopidogrel.

Bivalirudin showed a reduced risk of bleeding compared to a heparin-based anticoagulant strategy in patients with moderate and high risk acute coronary syndromes undergoing early invasive management.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of adult patients with acute coronary syndromes (ACS: unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention. Bivalirudin should be administered with aspirin and clopidogrel.

Dosing information

Start with an intravenous bolus of 0.1mg/kg followed by an infusion of 0.25mg/kg/hour. Subsequent dosing varies according to the intervention (medical, percutaneous or surgical) undertaken for ACS.

Product availability date

January 2008

Summary of evidence on comparative efficacy

Bivalirudin is direct inhibitor of thrombin. It was originally licensed as an anticoagulant for use in patients undergoing percutaneous coronary intervention (PCI) and the licence has been extended to include the treatment of ACS planned for urgent or early intervention.

The pivotal evidence for this indication comes from a multicentre, prospective randomised, open-label, parallel-group trial and the most relevant comparison is between 4,603 patients randomised to heparin (unfractionated heparin (UFH) or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor (GPI) and 4,612 randomised to bivalirudin alone (without GPI). Eligible patients were adults with moderate and high risk ACS. Angiography was performed in all patients within 72 hours of randomisation, followed by triage at the physician's discretion to further treatment (percutaneous, surgical, or medical). A third arm received bivalirudin and GPI but the results are not presented because the addition of GPI conferred no clinical advantage. All patients were recommended to receive clopidogrel or ticlopidine, though this, and the regimen used, was at the discretion of the investigator.

At 30-days' follow-up (\pm 5 days) three primary endpoints were tested sequentially in the following order for the comparison between bivalirudin alone and heparin/GPI: 1) superiority of the bleeding endpoint (major bleeding according to a trial-specific scale); 2) non-inferiority then superiority of a composite net clinical outcome endpoint; 3) non-inferiority then superiority of a composite ischaemic outcome endpoint. The non-inferiority margin was 25%. The ischaemic endpoint was a composite of death from any cause, MI or unplanned revascularisation for ischaemia. The net clinical outcome endpoint was a composite of the ischaemic and major bleeding outcomes. All analyses were on the intention to treat population and adjustment was made for multiple comparisons. One-year data are also available for the ischaemic and major bleeding outcomes.

The European Medicines Agency (EMA) considered bleeding to be a safety outcome and questioned the validity of the net clinical outcome therefore results are presented for the composite ischaemic endpoint only in this section. At 30-days, bivalirudin was non-inferior to heparin plus GPI for the incidence of this endpoint but there was a non-significant numerical advantage for heparin/GPI for the composite and all of its individual components (Table 1).

Table 1. Ischaemic clinical outcome data at 30-day follow up

Outcome	Heparin plus GPI (n=4,603)	Bivalirudin alone (n=4,612)	Relative risk bivalirudin versus heparin/GPI (95% CI)
Composite ischaemia, n (%)	334 (7.3)	360 (7.8)	1.08 (0.93 to 1.24)
Death from any cause	62 (1.3)	74 (1.6)	-
MI	227 (4.9)	248 (5.4)	-
Unplanned revascularisation for ischaemia	105 (2.3)	110 (2.4)	-

CI= confidence intervals GPI=glycoprotein IIb/IIIa inhibitor

At one year the rates of composite ischaemia were 15.4% and 16.2% for heparin/GPI and bivalirudin alone respectively, representing a relative risk of 1.06 (95% CI 0.95 to 1.17). Heparin/GPI was also numerically superior to bivalirudin for MI and revascularisation but not for death from any cause. None of these differences were significant.

Summary of evidence on comparative safety

Although defined as an efficacy variable, major bleeding was considered by the EMEA to be a safety outcome. It was reported both as a trial-specific scale and according to the Thrombolysis in Myocardial Infarction (TIMI) definition.

Table 2 Definitions of major bleeding

Trial-specific definition (30-day follow-up)	Thrombolysis in Myocardial Infarction (TIMI)
Cumulative occurrence within 25-35 days after randomisation of intracranial, retroperitoneal or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma with a diameter of at least 5cm, a reduction in haemoglobin levels of at least 3g/dL with an overt bleeding source or 4g/dL without, re-operation for bleeding or transfusion of a blood product. Unrelated to coronary artery bypass graft (CABG) surgery.	Intracranial bleeding or bleeding associated with haemoglobin decrease of >5g/dL (or a haematocrit decrease of 15%). Independent of CABG bleeding.

There were significant advantages for bivalirudin alone versus heparin/GPI for both scales, but the incidence rates and absolute difference were smaller in the TIMI analysis.

Table 3. Major bleeding outcome data at 30-day follow up

Outcome	Heparin plus GPI (n=4,603)	Bivalirudin alone (n=4,612)	Relative risk bivalirudin versus heparin/GPI (95% CI)
Trial-specific scale, n (%)	262 (5.7)	139 (3.0%)	0.53 (0.43 to 0.65)
Thrombolysis in Myocardial Infarction (TIMI) scale, n (%)	86 (1.9)	43 (0.9)	0.47 (CI not available)

CI= confidence intervals GPI=glycoprotein IIb/IIIa inhibitor

Other than for bleeding, the analysis of adverse events combined results from the bivalirudin alone and bivalirudin plus GPI arms. Up to the Day 30 visit, 416 (8.9%) heparin and 772 (8.6%) bivalirudin patients experienced one or more serious adverse events (SAEs, including

SAEs with an outcome of death). The system organ classes (SOCs) most commonly associated with SAEs up to the Day 30 visit were cardiac disorders, general disorders and administration site conditions, and infections and infestations (in $\geq 1.0\%$ of all heparin and bivalirudin patients). The overall incidence of SOC associated with SAEs up to the Day 30 visit was comparable for the heparin and bivalirudin treatment groups. More heparin than bivalirudin patients experienced cardiac disorder (3.4% versus 3.2%), respiratory, thoracic and mediastinal disorder (1.1% versus 0.9%), and vascular disorder (1.0% versus 0.8%) SAEs ($\geq 0.2\%$ difference between treatment groups), but the incidence of these events was low.

Summary of clinical effectiveness issues

The key efficacy outcome for registration was considered to be the composite ischaemic events for which bivalirudin alone was shown to be non-inferior but not superior to heparin/GPI at 30-days' follow-up. Efficacy was also similar between groups after one year. The EMEA considered the non-inferiority margin of 25% to be rather wide but noted that the one-year results were 'reassuringly tight' - effectively within a 15% margin.

The primary outcome of major bleeding was considered by the EMEA to be a safety outcome and significantly favoured bivalirudin alone over heparin/GPI. This advantage disappeared when bivalirudin was combined with GPI such that addition of GPI to bivalirudin was not considered to offer any clinical advantage.

Feedback and data obtained during expert consultation indicate that the trial design differs substantially from Scottish practice. For example, GPI are used more conservatively in Scottish practice (in about 44% of patients overall and less than 7% as an early intervention). Radial access is the default route for PCI in Scotland and is associated with a lower risk of bleeding than the femoral route used in 87% of patients in the trial. The trial-specific definition of major bleeding was argued to be more specific to ACS/PCI than the Thrombolysis in MI scale, but it was strongly influenced by access site bleeding, particularly haematoma, and the EMEA had reservations about its validity to reflect major bleeding. Major bleeding rates continued to favour bivalirudin using the TIMI scale and after exclusion of access site haematoma, but the incidence rates, and hence the absolute difference, were smaller than with the specific trial scale.

The pivotal trial incorporated a further randomisation in the heparin/GPI and bivalirudin/GPI arms. This was between routine 'up-stream' introduction of GPI and selective deferred use – only in patients undergoing PCI. The primary hypothesis of this analysis did not involve bivalirudin, however in the light of expert comment it is notable that deferred GPI was associated with a significantly reduced rate of major bleeding at 30 days. Over-representation of GPI use, particularly upstream, may have inflated the incidence of major bleeding in the heparin/GPI arm compared with Scottish practice.

About 64% of patients received heparin pre-randomisation, and the incidence was similar in all treatment arms, including those in which patients received bivalirudin.

Additional analyses showed that the results of the composite ischaemic endpoint were more favourable to bivalirudin, especially bivalirudin alone, in patients who also receive aspirin and clopidogrel and the bleeding advantage was retained in those patients. Thus the indication for bivalirudin specifies co-administration with those agents.

Bivalirudin was associated with a significant advantage over heparin and GPI for the net clinical benefit outcome. The EMEA did not consider this for registration purposes as it was

of the strong opinion that efficacy and safety variables should not be mixed in a single outcome. Nevertheless, with similar efficacy between bivalirudin alone and heparin/GPI and significantly reduced rates of bleeding, it reflects a net clinical advantage for bivalirudin when combined with aspirin and clopidogrel as licensed (but not when combined with GPI).

The trial was open-label but hard endpoints, including death and MI, were adjudicated by blinded assessors to minimise bias.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis, using a Markov model, to compare bivalirudin to heparin plus GPI in patients with unstable angina/non-ST segment elevation myocardial infarction before urgent/early angiography (within 24 hours of admission). The clinical data came from the main clinical study for a sub-group of patients being those receiving clopidogrel / ticlopidine before or after angiography. The utility values came from a study of patients in England discharged with myocardial infarction. Resource use came mainly from the clinical study and the unit costs used Scottish Reference Costs for most values. Life expectancy came from English registry data. A life time horizon was assumed.

The incremental cost effectiveness ratio (ICER) was £11,041/QALY for the bivalirudin strategy compared to the heparin based strategy. This fell to £5,590/QALY for a sub-group with at least two risk factors for bleeding. Sensitivity analyses showed the result was robust to the factors tested and 73% of the ICERs were forecast to fall under a £20,000 threshold.

There were some concerns that these results did not reflect the patient group likely to be treated in Scotland or take account of the predominant puncture routes used in Scotland (radial rather than femoral). As such, the manufacturer provided some additional analyses to address these issues. The results indicated that the cost-effectiveness of upstream (pre-PCI) bivalirudin use, compared to upstream heparin plus GPI use in those patients who currently receive upstream GPI is £17,584 per QALY or less. Where this analysis was adjusted to take account of radial puncture routes and associated different bleeding rates the cost per QALY was £19,376 or less.

Given these results the economic case was demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guidelines on in-hospital management of ACS in 2007. Initial management varies according to features (including ST-segment elevation) at presentation and may include low molecular weight heparin or fondaparinux as anticoagulant therapy. No specific recommendation is made for use of direct thrombin inhibitors, though it is acknowledged that they have comparative efficacy to other anticoagulants with a decreased risk of bleeding.

The European Society of Cardiology published guidelines for non-ST elevation ACS in June 2007, and recommendations for urgent anticoagulant therapy include bivalirudin.

Additional information: previous SMC advice

Following a full submission, the Scottish Medicines Consortium issued advice in March 2005: bivalirudin (Angiox[®]) is accepted for restricted use within NHS Scotland as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), including percutaneous transluminal coronary angioplasty (PTCA) procedures like angioplasty and balloon angioplasty and PTCA with stenting. It is restricted to patients who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa antagonist. In these patients bivalirudin monotherapy may be a suitable alternative. It should not be used as an alternative to unfractionated heparin alone.

Additional information: comparators

Anticoagulant therapies recommended by SIGN guidelines for ACS are fondaparinux and LMWH, and enoxaparin is the only LMWH licensed in this indication. Unfractionated heparin is a possible (unlicensed) alternative. Bivalirudin is not recommended in combination with a GPI however, GPIs may be administered with other anticoagulant therapy. In some cases the cost of a GPI should be added to the cost of these comparator anticoagulant drugs, but practice varies. For information, costs are given for two GPIs with the related indication prevention of myocardial infarction in patients with unstable angina.

Cost of relevant comparators

Drug	Dose regimen	Cost per day (£)
Anticoagulant therapy		
bivalirudin	0.1 mg/kg bolus followed by infusion of 0.25mg/kg/hour.	620
enoxaparin	1mg/kg every 12 hours by subcutaneous injection	11
fondaparinux	2.5mg once daily by subcutaneous injection	6.66
UFH	60 U/kg bolus followed by infusion of 12 IU/kg/h*	1.50
GPI therapy		
tirofiban	Intravenous infusion of 32 ml/hour for 30 minutes then 8 ml/hour	146-161**
eptifibatide	Intavenous bolus of 180 microgram/kg then infusion of 2 micrograms/kg/minute	151

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18th August 2008. Weight-based dosing assumes a 70kg individual

*Dose used in pivotal trial **Costs using concentrate for solution for infusion and solution for infusion respectively

The costings above are for early treatment in the period leading up to angiography and a definitive intervention (percutaneous, surgical or medical). Patients will receive further treatment to cover this intervention, but are not considered here since, for example, the use of bivalirudin during PCI is the subject of different indication. The duration of this early

period is likely to vary but the mean duration prior to intervention was less than a day in the pivotal trial. Costs for concurrent medications such as platelet aggregation inhibitors other than GPI are not included.

Enoxaparin is costed at the dose licensed for unstable angina and non-Q-wave MI but is the subject of a broader recommendation in SIGN ACS guidelines.

Additional information: budget impact

The changing pattern of care for patients with ACS/NSTEMI makes assessment of the overall budget impact very difficult. If used instead of GPI, the budget impact per patient treated is very modest, and could be neutral if some costs associated with bleeding complications are avoided. Patient numbers in Scotland are predicted to fall from around 10000 in 2008 to 6500 by 2013.

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 17 October 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.

The undernoted references were supplied with the submission.

Stone GW, Ware JH, Bertrand ME et al. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. JAMA. 2007;298(21):2497-506.

Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16

European Medicines Agency. Angiox European Public Assessment Report EMEA/H/C/562/II/08 November 2007. <http://www.emea.europa.eu>