THE **MEDICINES** COMPANY®

07 January 2013

Direct Healthcare Professional Communication on approved dosing regimens for Angiox (bivalirudin)▼ for PCI, following reports of inappropriate use.

Dear Healthcare Professional,

Summary:

- Healthcare professionals should ensure that approved dosing for Angiox is followed; in patients undergoing percutaneous coronary intervention (PCI) an intravenous (IV) bolus injection of 0.75 mg/kg body weight should be followed immediately by an IV infusion at 1.75 mg/kg/hour for at least the duration of the PCI.

- Failure to immediately initiate an IV infusion following the IV bolus will result in sub-therapeutic plasma concentrations of bivalirudin.

- Renal Impairment: The IV infusion dose should be reduced to 1.4 mg/kg/hour in patients with moderate renal impairment (Glomerular Filtration Rate [GFR], 30-59 mL/min) and activated clotting time (ACT) monitored.

- Bivalirudin is contra-indicated in patients with severe renal impairment and in dialysis-dependent patients.

This communication has been agreed with the European Medicines Agency.

Further information on the safety concern

For patients undergoing PCI, bivalirudin MUST be administered initially as an IV bolus followed immediately by an infusion. This dosing regimen is required to achieve and maintain the plasma concentration required for effective ischaemic protection during PCI. Based on the short half-life of bivalirudin (25 minutes), failure to initiate an infusion following the Angiox bolus will result in a sub-therapeutic plasma concentration within minutes.

Post-marketing data suggest that some patients are only treated with an IV bolus dose of Angiox, without the required subsequent IV infusion. Such underdosing could lead to suboptimal ischaemic protection during the procedure.

The Medicines Company UK Ltd
115L Milton Park, Abingdon, Oxfordshire, OX14 4SA Tel: +44 (0)1235 448500 Fax: +44 (0)1235 835561 www.themedicinescompany.com
Registered in England No.3484279 VAT Registration No. 700 4204 05

The approved dose of patients undergoing PCI, including primary PCI, is an IV bolus of 0.75 mg/kg body weight, immediately followed by an IV infusion at a rate of 1.75 mg/kg/hour for at least the duration of the procedure. The 1.75 mg/kg/hour IV infusion may be continued for up to 4 hours post-PCI as clinically warranted. After this, a reduced IV infusion dose of 0.25 mg/kg/hour may be continued for up to 12 hours as clinically necessary. Patients should be carefully monitored following primary PCI for signs and symptoms consistent with myocardial ischaemia.

Approximately 20% of bivalirudin is excreted via the kidneys and in patients with renal impairment the half-life of bivalirudin may be prolonged. Therefore, the use of Angiox is contraindicated in patients with severe renal impairment (GFR <30 ml/min) and in dialysis-dependent patients.

In patients with moderate renal impairment (GFR 30-59 ml/min) the IV infusion rate should be reduced to 1.4 mg/kg/hour, and the ACT monitored during the procedure. The IV bolus dose remains 0.75 mg/kg for all patients.

Further information to Healthcare Professionals

Bivalirudin (Angiox) is indicated as an anticoagulant in adult patients undergoing PCI, including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Bivalirudin is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention. Angiox should be administered with aspirin and clopidogrel.

Dosing recommendations for patients with unstable angina/non-ST segment elevation myocardial infarction are provided in the Summary of Product Characteristics, annexed to this letter.

The use of the Angiox dosing cards (included with this letter) is recommended as a quick reference guide. Please see Annex for full information on dosing from the Angiox Summary of Product Characteristics (SPC).

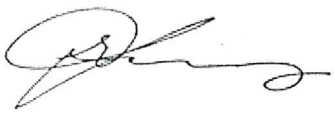
Reporting suspected adverse drug reactions

Call for reporting

Any suspected adverse reaction to Angiox should be reported to the Irish Medicines Board (IMB) on (01) 676 4971 or online at http://www.imb.ie/EN/Safety--Quality/Online-Forms.aspx or to The Medicines Company Global Health Science Center medical information line at 00800 843 633 26 or + 41 44 828 1084. **Fax:** + 41 448281082 **Email:** medical.information@themedco.com

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Sincerely,



Efthymios N. Deliargyris, MD, FACC, FESC, FSCAI
Global Medical Director
The Medicines Company