European Medicines Agency

London, 29 May 2009
EMEA/328956/2009

Public statement
on possible interaction between clopidogrel and proton pump inhibitors

The European Medicines Agency is aware of studies suggesting that clopidogrel may be less effective in patients also receiving some types of proton pump inhibitor (PPI). This could result in patients being at an increased risk of thrombotic events, including acute myocardial infarction (heart attack).

Clopidogrel is an antiplatelet medicine that is used to prevent a further heart attack in patients who have recently had an attack. It is also used in patients who have had other problems caused by blood clots, such as ischaemic strokes (non-bleeding strokes) or acute coronary syndromes. In the European Union, clopidogrel is authorised as Plavix, Iscover, Clopidogrel BMS and Clopidogrel Winthrop.

PPIs are medicines that are used to prevent and treat heartburn and stomach ulcers. They include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. As heartburn and stomach ulcers can occur as side effects of clopidogrel, patients taking clopidogrel often take PPIs to prevent or ease these symptoms. Evidence is emerging that most PPIs slow down the conversion of clopidogrel into its biologically active form in the body. This means that PPIs may reduce the effect of clopidogrel, resulting in an increased risk of heart attack. This interaction is more pronounced in patients who, for genetic reasons, are less able to convert clopidogrel into its biologically active form – so-called 'CYP2C19 poor metabolisers'.

In March 2009, the *Journal of the Canadian Medical Association* published a study on the interaction between PPIs and clopidogrel[1]. This study investigated the medical records of 2,791 patients who had been treated with clopidogrel, comparing the 734 who had another heart attack and the remaining 2,057 who did not. The study found a 40% increased risk of a further heart attack in the patients who were taking a PPI other than pantoprazole: 20% of the patients taking one of these PPIs had a further heart attack (148 out of 734), compared with 15% of those not taking a PPI (299 out of 2,057).

In addition, several other published studies, including pharmacokinetic studies, clinical trials and observational studies, also suggest a clinically significant interaction between clopidogrel and PPIs. The available studies suggest that this interaction affects all members of the PPI class.

Conclusions
Following review of all of the available data, the Agency's Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP) have recommended that the product information for all clopidogrel-containing medicines be amended to include information on the interaction between PPIs, stating that the concomitant use of PPIs should be avoided unless absolutely necessary.

The CHMP has asked the marketing authorisation holders for the clopidogrel-containing medicines to implement these changes to the product information via variation procedures.

Noël Wathion
Head of Unit for the Post-Authorisation Evaluation
of Medicinal Products for Human use

[1] Juulinck, D., Gomes, T., Ko, D. *et al*, 'A population-based study of the drug interaction between proton pump inhibitors and clopidogrel.', *CMAJ*, 180(7), pp. 713-718.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 09
E-mail: mail@emea.europa.eu http://www.emea.europa.eu