



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 receiving 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. Clopidogrel is converted from an inactive form to an active form in the body. 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.

The new concern relates to several recently published studies examining clinical outcomes of clopidogrel users. Taken together, these studies suggest that a significant interaction might occur between clopidogrel and members of the PPI class of medicines, making clopidogrel less effective when given with these medicines.

One possible explanation for this observation is that some PPIs prevent the conversion of clopidogrel into its biologically active form in the body, reducing the effectiveness of clopidogrel and increasing the risk of heart attack or other conditions involving harmful clotting (e.g. strokes). However, as different PPIs have different capacity to affect the metabolism of clopidogrel and as the outcome studies have not fully reflected the different effect of PPIs on activation of clopidogrel, there may be more than one explanation for the effect of this class of medicines on clopidogrel.

Taking all the data into account, 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 should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary. Accordingly, the marketing authorisation holders for the clopidogrel-containing medicines will shortly be submitting variation applications in order to amend the product information.

Furthermore, CHMP recommended that further information is needed in relation to the inhibition of clopidogrel metabolism by other medicines, and in relation to the implications of genetic variation which results in a small proportion of individuals (so called 'CYP2C19 poor metabolisers') being unable to fully convert clopidogrel to its active form, regardless of interactions with other medicines.

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