

**Notice Information: - Advisory
05 June 2009**

Part 1. Product Information

- a) Title: Updated Information on Possible Interaction between Clopidogrel and Proton Pump Inhibitors.
- b) Product Name/Type: Plavix
- c) Active Substance: Clopidogrel

Part 2. Problem/Issue

- a) Problem/Issue: Further to the publication of interim recommendations on avoiding concomitant use of clopidogrel and PPIs, the IMB wishes to update healthcare professionals and the public regarding the outcome of the EU review of this potential interaction. Following review of all of the available data, the European Medicines 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.

Part 3. Background Information

a) Background Information:

Clopidogrel is an antiplatelet drug authorized for the prevention of atherothrombotic events in patients suffering from myocardial infarction (heart attack), ischaemic stroke or acute coronary syndrome, or those at risk of these problems. Clopidogrel is a “pro-drug” which means that it has to be metabolized by the body before it can be biologically active and have the effect of preventing blood clots.

As previously communicated, the IMB is aware of studies suggesting that clopidogrel may be less effective in patients also receiving some types of proton pump inhibitor (PPI).

Proton pump inhibitors include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. PPIs decrease stomach acid and are used to treat frequent heartburn and stomach ulcers. As heartburn and stomach ulcers can occur as side effects of clopidogrel, patients taking clopidogrel often take PPIs to prevent or ease these symptoms.

Clopidogrel is metabolised by the liver to an active molecule that inhibits platelet aggregation however evidence is emerging that some PPIs inhibit this pathway. 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’.

The Journal of the Canadian Medical Association has published the results of a population-based study that aimed to assess the clinical importance of the interaction between proton pump inhibitors (PPIs) and clopidogrel. This research reviewed database records for 13,636 patients who were started on treatment with clopidogrel after an acute myocardial infarction between 2002 and 2007. 782 of these patients were readmitted within 90 days with a second event. Of this latter group, 734 patients were matched with 2,057 controls and analyses were performed for associations between usage of a PPI and cardiac events. Patients who were readmitted were more likely to have co-morbidities such as heart failure, diabetes and renal failure. Despite this additional disease burden they were less likely to be prescribed ACE inhibitors, beta-blockers or statins.

After correcting for many factors, this analysis found an increased risk in readmission related to cardiac events in current users of PPIs (adju

(adjusted odds ratio 1.27, 95% CI 1.03-1.57). Further analysis found no correlation between readmission and H2-receptor antagonists or in readmission among non-users of clopidogrel.

Notable limitations of this study are the lack of data for some important cardiac risk factors including smoking status, blood pressure and lipid levels. Non-prescription medication data were also unavailable for the analysis. The authors conclude that, "concomitant treatment with clopidogrel and proton pump inhibitors should be minimised".

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.

Part 4. Action to be taken

a) Action to be taken:

IMB Advice for Healthcare Professionals

- Healthcare professionals should be aware of this interaction and the potential to increase cardiac events such as acute myocardial infarction.
- Healthcare professionals should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel. The risk-benefit of continuing treatment with a PPI should be considered by the prescribing physician and the concomitant use of these medicines should be avoided unless essential.
- Healthcare professionals should continue to prescribe clopidogrel in line with its licensed indications and patients should continue to take clopidogrel as directed.
- PPIs should be prescribed strictly in line with their licensed indications.
- Healthcare professionals should continue to report suspected adverse reactions associated with clopidogrel/PPIs to the Irish Medicines Board.

IMB Advice for Patients

- Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a Proton Pump Inhibitor (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole.).