Plavix 75 mg film-coated tablets EU/1/98/069/001a
Plavix 300 mg film-coated tablets- EU/1/98/069/009
DuoPlavin 75 mg / 75 mg film-coated tablets EU/1/198/619/002

Direct Healthcare Professional Communication on the association of clopidogrel with acquired haemophilia

23 August 2013

Dear Healthcare Professional,

Summary
A small number of cases of acquired haemophilia associated with clopidogrel treatment in individuals with no previous history of abnormal haemostasis have been reported.

- Acquired haemophilia must be promptly recognised to minimise the time the patient is at risk of bleeding and avoid major bleeding.
- In case of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered.
- Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, clopidogrel should be discontinued and invasive procedures should be avoided.

The information provided in this letter has been reviewed and endorsed by the European Medicines Agency (EMA) and the Irish Medicines Board.

Further information on the safety concern
Acquired haemophilia A is a very rare autoimmune disease. The incidence is estimated in the literature at 1 to 4 patients per million, per year. Morbidity and mortality are high due to the often older age of patients, underlying diseases, bleeding and toxic effect of immunosuppressant treatment.

11 case reports of acquired haemophilia A and 1 case report of acquired haemophilia B associated with clopidogrel treatment have been transmitted to sanofi or published in the literature since the launch of the product:

- These involved 8 males, 2 females and the gender was unknown in 2 patients.
- The age range was between 65 and 81 years.
- Time to onset (where reported) ranged from a few days to 4 months after starting clopidogrel treatment.
- Two cases were life-threatening and none had a fatal outcome.
- Reaction abated after clopidogrel discontinuation and corrective treatment in 5 out of the 8 patients for which the information on the outcome was made available.

Product Information is being updated with information on this risk, in Section 4.4 (Special warnings and precautions for use) of the Summary of Product Characteristics (see enclosed for full product information):

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Based on the very small number of reports of acquired haemophilia in the context of very high use (over 153 million patients worldwide), the benefit/risk balance of clopidogrel is considered unchanged in the approved therapeutic indications (see enclosed for full details of the indications):

Clopidogrel is indicated for the prevention of atherothrombotic events in myocardial infarction, ischaemic stroke, established peripheral arterial disease, acute coronary syndrome including Non-ST segment elevation myocardial infarction and unstable angina, and ST segment elevation acute myocardial infarction with aspirin in medically treated patients eligible for thrombolytic therapy. Clopidogrel is also indicated in combination with aspirin for the prevention of atherothrombic and thromboembolic events in atrial fibrillation in patients unsuitable for vitamin K antagonist treatment.
The clopidogrel and aspirin fixed dose combination is indicated for the prevention of atherothrombotic events in patients already taking both clopidogrel and aspirin for Non-ST segment elevation myocardial infarction, unstable angina or ST segment elevation myocardial infarction in medically treated patients eligible for thrombolytic therapy.

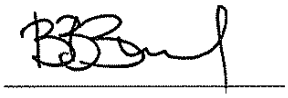
Call for reporting

Any adverse events experienced by your patients should be reported to Sanofi Ireland Ltd. Directly using the contact details below or to the Pharmacovigilance Section of the IMB using yellow-card reporting system, the on-line reporting function on the IMB website (www.imb.ie) or alternatively by contacting the IMB at 01 6764971.

Company contact point

For further information please contact:
Sanofi Ireland Ltd., 18 Riverwalk, Citywest Business Campus, Dublin 24
Tel: 01-4035600 Email address: IEmedinfo@sanofi.com

Yours sincerely,



Dr. Velichka Valcheva MD
Medical Director

Enclosed: Plavix® / DuoPlavin® Summary of Product Characteristics

List of literature references:

- Collins PW. Management of acquired haemophilia A. J Thromb Haemost 2011; 9 (Suppl. 1): 226–235.
- Haj M, Dasani H, Kundu S, Mohite U, Collins PW. Acquired haemophilia A may be associated with clopidogrel. BMJ 2004;329(7461):323
- Huth-Kühne A et al.. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009; 94:566-752.
- Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, Pellegrini F, Tengborn L, Lévesque H; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb.Haemost. 2012 Apr; 10(4): 622-31