02nd August 2013

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

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 Medicines Authority.

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:
o These involved 8 males, 2 females and the gender was unknown in 2 patients.
o The age range was between 65 and 81 years.
o Time to onset (where reported) ranged from a few days to 4 months after starting clopidogrel treatment.
o Two cases were life-threatening and none had a fatal outcome.
o 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 Annex 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 Annex 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.

3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805– Malta – Tel: (+356) 21 493 022 – Fax (+356) 21 493 024 – www.sanofi-aventis.com

Call for reporting:

Healthcare professionals should report any adverse events suspected to be associated with the use of Multaq to Sanofi-Aventis Malta Ltd., 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, fax 21493024

Alternatively any suspected adverse reactions can also be reported to
Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: www.medicinesauthority/adrportal.

Company contact point
If you have any questions or require additional information, please call Medical Information Services at Sanofi-Aventis Malta Ltd, 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, Fax: 21493024

Yours Sincerely

Graziella Gravino B. Pharm (Hons)
Head of Regulatory Affairs & Pharmacovigilance
Sanofi-Aventis Malta Ltd.

Appendix
I. Sections of the Product Information that have been revised
2. 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