EMA/411850/2014
London, 28 July 2014

Summary of the risk management plan (RMP) for Clopidogrel/Acetylsalicylic acid Teva (clopidogrel / acetylsalicylic acid)

This is a summary of the risk management plan (RMP) for Clopidogrel/Acetylsalicylic acid Teva, which details the measures to be taken in order to ensure that Clopidogrel/Acetylsalicylic acid Teva is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Clopidogrel/Acetylsalicylic acid Teva, which can be found on Clopidogrel/Acetylsalicylic acid Teva's EPAR page.

Overview of disease epidemiology

Clopidogrel/Acetylsalicylic acid Teva is a medicine used to prevent problems caused by blood clots, such as a heart attack, in patients who have a condition known as 'acute coronary syndrome'. This syndrome comprises various heart conditions, including myocardial infarction (heart attack) and unstable angina (a severe type of chest pain), brought on by sudden, reduced blood flow to the heart. Heart attack is one of the most common causes of mortality worldwide. Over seven million people every year die from a heart attack, accounting for 12.8% of all deaths. The likelihood of a heart attack increases with age for both sexes and is higher in men than in women.

Summary of treatment benefits

Clopidogrel/Acetylsalicylic acid Teva contains two active substances, clopidogrel and acetylsalicylic acid (known commonly as aspirin). It is used in adults who are already taking both clopidogrel and acetylsalicylic acid as separate tablets. The two active substances have been used together for a number of years. Results of 3 studies involving in total over 61,000 patients with acute coronary syndrome are available, which showed that the combination of clopidogrel and acetylsalicylic acid taken as separate tablets is more effective at preventing events such as heart attacks than acetylsalicylic acid alone.

Studies have also been conducted to show that the active substances in Clopidogrel/Acetylsalicylic acid Teva are absorbed in the body in the same way when taken in a single tablet as when the two medicines are taken separately. Combining both active substances in a single tablet simplifies treatment for patients as they will need to take fewer tablets.

Unknowns relating to treatment benefits

The combination of clopidogrel and acetylsalicylic acid has not been studied in subjects under 18 years old.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bleeding and haematological (blood) disorders, and increased risk of bleeding in certain patients	The combination of clopidogrel and acetylsalicylic acid prolongs bleeding time. Bleeding is the most common adverse event reported both in clinical studies (typically affecting up to about 1 patient in 10) as well as in the post-marketing experience, where it was mostly reported during the first month of treatment. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported. The combination of acetylsalicylic acid and clopidogrel has been shown to increase the risk of major bleeding in patients with recent transient ischaemic attack (reduced blood supply to the brain) or stroke, who are at high risk of recurrent ischaemic events.	Doctors should inform patients that it might take longer than usual to stop bleeding when they take Clopidogrel/Acetylsalicylic acid Teva. Doctors should carefully observe patients for any signs of bleeding, especially during the first weeks of treatment and/or after invasive heart procedures or surgery. They should promptly consider blood cell count and/or other appropriate testing whenever symptoms suggestive of bleeding arise during the course of treatment. Patients should inform physicians and dentists that they are taking Clopidogrel/Acetylsalicylic acid Teva before any surgery is scheduled and before any new medicine is taken. Patients should report any unusual bleeding (site or duration) to their treating doctor. Because clopidogrel and acetylsalicylic acid are antiplatelet agents (that prevents blood clots), Clopidogrel/Acetylsalicylic acid Teva should be used with caution in patients at risk of increased bleeding from trauma, surgery (including dental surgery) or other conditions, and in patients receiving treatment with some other medicines such as so-called NSAIDs (including Cox-2 inhibitors), heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or thrombolytics. Clopidogrel/Acetylsalicylic acid Teva is not recommended with oral anticoagulants (such as warfarin) since it may increase the intensity of bleeding. In case of planned surgery, doctors should review treatment with Clopidogrel/Acetylsalicylic acid Teva and consider using a single antiplatelet agent. If patients must temporarily stop

Risk	What is known	Preventability
		antiplatelet therapy, Clopidogrel/Acetylsalicylic acid Teva should be discontinued 7 days prior to surgery. Clopidogrel/Acetylsalicylic acid Teva must not be used in patients who are actively bleeding such as patients with a peptic ulcer or bleeding in the brain. Clopidogrel/Acetylsalicylic acid Teva should be used with caution in patients with a history of ulcers, bleeding in the stomach or bowels or minor upper gastrointestinal symptoms (such as stomach pain, heartburn, nausea and vomiting) that may be due to gastric ulceration which could lead to bleeding in the stomach. Physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous gastrointestinal symptoms. Patients should be told about the signs and symptoms of gastrointestinal side effects and that they should inform their doctor if they occur. Patients with a confirmed diagnosis of acquired haemophilia (an inherited bleeding disorder) should be managed and treated by specialists, and Clopidogrel/Acetylsalicylic acid Teva should be discontinued.
Hypersensitivity (allergic) reactions	Patients with a history of asthma or allergic disorders are at increased risk of hypersensitivity reactions. Hypersensitivity reactions may also occur in patients hypersensitive to other medicines of the class 'thienopyridines', such as ticlopidine and prasugrel. Hypersensitivity reactions including breathing difficulties sometimes associated with cough, generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort leading to fainting), swelling in the mouth, blisters of the skin and skin allergies	Due to its acetylsalicylic acid content, Clopidogrel/Acetylsalicylic acid Teva must not be used in patients hypersensitive to non-steroidal anti-inflammatory drugs (NSAIDs, such as acetylsalicylic acid) or who have a medical condition that includes a combination of asthma, rhinitis (stuffy and runny nose) and nasal polyps (growths in the lining of the nose). Clopidogrel/Acetylsalicylic acid Teva should be used with caution in patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions. Patients should talk to their doctor or pharmacist before taking

Risk	What is known	Preventability
	have been reported with the use of clopidogrel and acetylsalicylic acid.	Clopidogrel/Acetylsalicylic acid Teva if they have a history of allergy to any medicine used to treat their disease.
Thrombotic thrombocytopenic purpura due to clopidogrel	Thrombotic thrombocytopenic purpura is a condition that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice). Thrombotic thrombocytopenic purpura has been reported very rarely (affecting less than 1 patient in 10,000) following the use of clopidogrel, sometimes after short use.	Not preventable and prompt treatment is important. Doctors may carry out blood tests to help diagnose thrombotic thrombocytopenic purpura.
Reduced effects of clopidogrel in 'poor CYP2C19 metabolisers'	Clopidogrel is transformed in the liver into its active form. Some people transform clopidogrel more slowly than the majority of the population. They are known as 'poor CYP2C19 metabolisers'. In these patients, recommended doses of clopidogrel produce less of the active form and have less effect in preventing blood clots.	Tests are available to identify patients who are poor CYP2C19 metabolisers.
Aggravation of gout due to acetylsalicylic acid	Gout is a condition of painful, swollen joints caused by deposits of uric acid crystals. Acetylsalicylic acid increases the amount of uric acid in the blood, aggravating gout.	Clopidogrel/Acetylsalicylic acid Teva should be used with caution in patients with gout since low doses of acetylsalicylic acid increase the amount of uric acid in the blood. Patients should inform their doctors if they have gout before taking Clopidogrel/Acetylsalicylic acid Teva.
Liver impairment due to acetylsalicylic acid	Liver injury and elevation of liver enzymes have been reported in the literature for acetylsalicylic acid with unknown frequency. Acute liver failure, hepatitis, and abnormal liver function test have been reported very rarely with the combination of clopidogrel and acetylsalicylic acid.	Patients should tell their doctor if they have liver disease before taking Clopidogrel/Acetylsalicylic acid Teva. Patients who have severe liver disease must not take Clopidogrel/Acetylsalicylic acid Teva.

Risk	What is known	Preventability
Kidney impairment due to acetylsalicylic acid	Reports in the literature indicate that acute kidney disease is associated with unknown frequency with the use of acetylsalicylic acid. Inflammation of the glomeruli (small filtering units in the kidney) or the small blood vessels in the kidneys (glomerulonephritis) has been reported very rarely with the combination of clopidogrel and acetylsalicylic acid.	Patients should tell their doctor if they have kidney disease before taking Clopidogrel/Acetylsalicylic acid Teva. Patients who have severe kidney disease must not take Clopidogrel/Acetylsalicylic acid Teva.
Eosinophilic pneumonia due to clopidogrel	Eosinophilic pneumonia is a lung disease in which white blood cells called 'eosinophils' accumulate in the lungs. Eosinophilic pneumonia has been reporeted very rarely with the combination of clopidogrel and acetylsalicylic acid.	Patients should tell their doctor if they experience fever and breathing difficulties sometimes associated with cough.
Bone marrow toxicity due to interaction with methotrexate	Methotrexate is a medicine used to treat severe joint disease (such as rheumatoid arthritis) or skin disease (such as psoriasis). When used at doses higher than 20 mg/week, it should be used with caution with the combination of clopidogrel and acetylsalicylic acid as this combination can block the elimination of methotrexate via the kidneys. This may lead to damage to the bone marrow where new blood cells are formed.	Patients should tell their doctor if they take methotrexate. Doctors should use Clopidogrel/Acetylsalicylic acid Teva with caution in these patients.

Important potential risks

Risk	What is known
Reye' s syndrome in children below 18 years of age, due to acetylsalicylic acid	There is a possible association between the use of acetylsalicylic acid in children or adolescents under 18 years old with a viral infection and the development of Reye's syndrome. Reye's syndrome is a very rare disease which can be fatal. Clopidogrel/Acetylsalicylic acid Teva is not indicated for children and adolescents under 18 years.
Reduced effects of clopidogrel when used together with medicines known as 'strong or moderate	Since clopidogrel is transformed into its active form partly by the enzyme CYP2C19 in the liver, use of medicines known as 'strong or moderate inhibitors of CYP2C19' that block the

Risk	What is known
inhibitors of CYP2C19' (such as omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol)	activity of this enzyme would be expected to result in reduced levels of the active form of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of these medicines should be discouraged.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	Clopidogrel/Acetylsalicylic acid Teva must not be used during the last 3 months of pregnancy, and it is preferable not to take this medicine during the first 6 months of pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage, and of cardiac malformation and gastroschisis (a defect in the abdominal wall) of the fetus after use of a 'prostaglandin synthesis inhibitor' such as acetylsalicylic acid in early pregnancy. It is unknown whether clopidogrel passes into human breast milk. Acetylsalicylic acid and its metabolites pass in limited amounts into human milk. Breastfeeding should be discontinued during treatment with the combination of clopidogrel and acetylsalicylic acid.
Interaction between acetylsalicylic acid and medicines known as NSAIDs (non-steroidal anti-inflammatory drugs, usually used to treat painful and/or inflammatory conditions of muscles or joints)	Experimental data suggest that some NSAIDs (celecoxib, dipyrone (its active form), ibuprofen, flufenamic acid, naproxen, nimesulide, oxaprozin, and piroxicam) may interfere with the antiplatelet effect of acetylsalicylic acid. Clinical implications of this observation are unknown.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Clopidogrel/Acetylsalicylic acid Teva can be found on Clopidogrel/Acetylsalicylic acid Teva's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

Not applicable.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 07-2014.