VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acetylsalicylic acid is a medicine which is used in adults over 16-years to prevent the risks of clots forming in the blood (antiplatelet medication). This reduces the risk of patients having a stroke or a heart attack (myocardial infarction). This medication is also used to prevent blockage during heart surgery (Coronary Artery Bypass), or in patients with chest pain (angina pectoris). This medication works by reducing the activation of platelets in the blood, meaning that the bloods ability to clot will be decreased.

Heart attack (Myocardial infarction)

Heart attack is one of the major causes of death of adults in developing countries. This is due to the changes in life style and the increased life expectancy. It is rare in the child and adolescent population and the risk of heart attack increases with age, with most patients who develop it over 60-years of age.

Heart Disease (Cardiovascular disease)

Heart disease accounts for 25-50% of deaths worldwide depending on the level of economic development. Risks that can cause heart disease include smoking, diabetes, obesity and poor diet and life style.

Chest pain (Angina pectoris)

Angina pectoris is chest pain which is caused when the blood supply to the heart muscles is restricted. The prevalence of angina rises with increasing age, with the mean age of onset roughly 62 years. Although angina is a manageable disease, around 4.8% of patients with angina subsequently die from coronary heart disease (disease affecting the blood vessels that supply the heart) after five years. Angina is more prominent in the western world as a result of the westernized diet and subsequently increased smoking, obesity and other risk factors.

Coronary artery disease

Coronary artery disease is caused by the narrowing or blocking of the coronary artery (blood vessel within the heart) which causes an impaired blood flow. Coronary artery disease is a major cause of death and disability in developing countries. Factors that can increase the risk of developing coronary artery disease include diet, lack of exercise, smoking and age.

“Mini”Stroke (Transient ischaemic attacks)

”Mini” stroke is a temporary inadequacy of blood supply in part of the brain that presents similarly to a stroke but it is reversible. The duration of a”mini” stroke is no longer than 24 hours. ”Mini” stroke is more likely to occur in patients over 60-years of age. Incidents of ”mini” stroke are decreasing, this is thought to be due to better treatment and control of high blood pressure. The risk factors for”mini” stroke are diet, lack of exercise, smoking and age.

Stroke (Ischaemic cerebrovascular accidents)

Ischaemic cerebrovascular accident is caused when there is an interruption in the blood supply within the brain due to a blood clot in the artery which supplies blood to the brain. Risk factors associated with strokes are age, smoking, diet, lack of exercise and family history.

VI.2.2 Summary of treatment benefits

Heart attack (Myocardial infarction)

In patients who have had a heart attack or who are at risk of developing a heart attack, the protective effect of acetylsalicylic acid have been investigated and found to achieve 20% reduction in both death and re-infarction. A study of 19,288 patients with suspected heart attack where given antiplatelet therapy for one month, which resulted in 38 fewer vascular events per 100 treated patients.

Prevention of graft occlusion after aorta-coronary bypass grafting
An aorta-coronary bypass grafting is surgery provided to treat coronary heart disease (blood vessels in the heart narrowing or blocking). Acetylsalicylic acid can be given following this surgery to prevent a bypass graft occlusion (blockage) vessels blocking. Improved one year post coronary bypass graft remaining unobstructed can be achieved by acetylsalicylic acid in doses of 50mg to 1000mg daily. A bypass graft blockage can either occur early (in the first week) or late (after the first week). An early blockage can be due to surgical factors whereas late blockage is more likely to be caused by atherosclerosis (disease of the arteries). Remarkably, trials with antiplatelet drugs in coronary surgery, in which acetylsalicylic acid was given on the first postoperative day, showed strong benefit of acetylsalicylic acid on the bypass graft remaining unobstructed, but those in which acetylsalicylic acid was begun on the third postoperative day or later, did not.

Chest pain (Angina pectoris)
One study showed a 33% risk reduction of vascular events (events relating to blood vessels) following antiplatelet therapy in patients with stable angina pectoris. A Swedish study involved 2035 patients with stable angina who either received 75mg acetylsalicylic acid plus sotalol (medication for treatment of heart problems) or a dummy pill (placebo) plus sotalol. The acetylsalicylic acid group had a 34% reduction in heart attacks and sudden death.

Other cardiovascular indications (relating to the heart and blood vessels)
Antiplatelet therapy had a risk reduction on vascular events (events relating to blood vessels) of 53% among patients who had coronary angioplasty (non-surgical procedure which relieves narrowing and blockage of the blood vessels in the heart) and of 23% among patients with peripheral arterial disease (a disease where plaque builds up in the blood vessels which carry blood to the organs or limbs).
One study suggested that antiplatelet therapy should be used on a wider range of high risk patients with heart problems due to findings that were reliable and roughly similar to those in patients with the above heart problems.

"Mini" stroke (Transient ischaemic attacks) and Stroke (Ischaemic cerebrovascular accidents)
There is clear evidence from studies that antiplatelet therapy prevents or delays about a quarter of serious events relating to blood vessels in patients who are at high risk because they already have clinical manifestations of vascular disease, including patients with a history of "mini" stroke and stroke.

VI.2.3 Unknowns relating to treatment benefits
Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in patients with kidney injury (Use in patients with severe renal impairment)	Acetylsalicylic acid should be used with caution in patients with kidney injury	A patient's kidney function should be monitored by their doctor

Risk	What is known	Preventability
Use in patients with liver injury (Use in patients with severe hepatic impairment)	Acetylsalicylic acid should be used with caution in patients with liver injury	Liver function tests should be performed regularly in patients presenting with slight or moderate liver injury
Use in elderly patients	Elderly patients are at greater risk of developing side effects.	Elderly patients should consult your doctor or healthcare professional prior to using acetylsalicylic acid
Use in children and adolescents under 16 years	Acetylsalicylic acid is known to contribute to the factors in the causation of Reye's Syndrome (a life threatening metabolic disorder).	Do not administer to patients under 16 years of age unless under medical supervision.
Use in patients with known allergies to the ingredients within this product (Use in patients with a known hypersensitivity to salicylic acid compounds)	Some patients may be allergic to the ingredients within acetylsalicylic acid.	Do not use if you have a known allergy to salicylic acid compounds
Decreased ability for blood to clot (Increased anticoagulant effect) and risk of bleeding.	Acetylsalicylic acid is known to cause an increased risk of bleeding. The risk may be increased in patients with a blood clotting problem such as haemophilia. Acetylsalicylic acid is absorbed quickly and completely in the digestive tract, as such there is an increased risk of bleeding within the stomach.	To prevent bleeding within the stomach (gastric bleeding), the tablet should be taken with food. This medicine should not be used in patients with a blood clotting problem.
Increased risk of bleeding and ulceration within the stomach or intestine (gastrointestinal bleeding)	Acetylsalicylic acid is known to cause in increased risk of bleeding. The risk may be increased in patients with a blood clotting problem such as haemophilia. Acetylsalicylic acid is absorbed quickly and completely in the digestive tract, as such there is an increased risk of bleeding within the stomach.	To prevent bleeding within the stomach (gastric bleeding), the tablet should be taken with food. This medicine should not be used in patients with a blood clotting problem.
Use in patients with pre-existing asthma, hay fever, nasal polyps or chronic respiratory disease	Acetylsalicylic acid may cause bronchospasms (breathing problems, caused by the narrowing of the bronchi within the lungs) in patients who suffer from asthma, hay	Only use under medical supervision if you have pre-existing asthma, hay fever, nasal polyps or chronic respiratory disease

Risk	What is known	Preventability
	fever, nasal polyps or chronic respiratory disease	
Steven-Johnsons syndrome or Lyell's syndrome (life threatening skin conditions)	Steven-Johnsons syndrome or Lyell's syndrome have rarely been reported with use of acetylsalicylic acid.	Stop use of acetylsalicylic acid immediately if a rash appears during treatment.
Interactions with other medication causing an increased risk of certain side effects (Clinically relevant drug-drug interactions causing alteration in blood levels; gastrointestinal bleeding, ulceration, nephrotoxicity, haematological and neurotoxicity)	Acetylsalicylic acid is known to interact with the before mentioned drugs and this could cause an increased risk of the following side effects: • alteration in the levels of acetylsalysilci acid within the blood • bleeding or ulceration within the stomach or intestine • Medication poisoning (nephrotoxicity, haematological and neurotoxicity)	Do not take acetylsalicylic acid with the before mentioned drugs unless under medical supervision.
Concomitant use with methotrexate (drug used for the treatment of cancer and autoimmune disease)	The use of acetylsalicylic acid and methotrexate could cause increased bleeding side effects	Do not use methotrexate (at doses >15mg weekly) and acetylsalicylic acid together.
Use during breastfeeding	Once broken down in the body acetylsalicylic acid may be passed through breast milk	Do not use acetylsalicylic acid for long periods of time or at high doses during breastfeeding.
Abnormally heavy bleeding at menstruation (Menorrhagia)	Acetylsalicylic acid is known to cause increased bleeding and should therefore not be used in patients who are suffering from abnormally heavy bleeding at menstruation	Acetylsalicylic acid is not recommended during an abnormally heavy menstruation as it may increase menstrual bleeding further.

Important potential risks

Risk	What is known
Reye's syndrome (life-threatening metabolic disorder in young children)	Acetylsalicylic acid may contribute to the development of Reye's Syndrome
Kidney and/or liver disorders (Moderate renal and/or hepatic disorders)	Acetylsalicylic acid should be used with caution in patients with moderately impaired kidney or liver function as treatment may result in worsening of kidney function.

Missing information

Risk	What is known
Safety during pregnancy	Acetylsalicylic acid should not be used during the third trimester of pregnancy. Any time during pregnancy the dose of acetylsalicylic acid should be kept as low as possible and for as short a period as possible.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for acetylsalicylic acid.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.2	08-10-2014	<u>Important identified risks</u> -Use in patients with severe renal impairment -Use in patients with severe hepatic impairment -Use in elderly patients -Use in children and adolescents under 16 years -Use in patients with a known hypersensitivity to salicylic acid compounds. -Increased anticoagulant effect and risk of bleeding -Increased risk of gastrointestinal bleeding and ulceration -Use in patients with pre-existing asthma, hay fever nasal polyps or chronic respiratory disease -Steven-Johnsons syndrome, Lyell's syndrome -Clinically relevant drug-drug interactions causing alteration in blood levels; gastrointestinal	RMP submitted in Hungary for new MA application. MA No.: OGYI-T-22761/01-07 OGYI-T-22761/08-14 OGYI-T-22761/15-21

Version	Date	Safety Concerns	Comment
		bleeding, ulceration, nephrotoxicity, haematological and neurotoxicity -Concomitant use with methotrexate -Use during breastfeeding -Menorrhagia <u>Important potential risks</u> -Reye's syndrome -Moderate renal and/or hepatic disorders <u>Missing information</u> -Safety during pregnancy	