VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

A stroke happens when blood flow to a part of the brain stops and is sometimes called a brain attack. If blood flow is stopped for longer than a few seconds, the brain cannot get blood and oxygen, leading to the death of brain cells and permanent damage. Ischemic stroke occurs when a blood vessel that supplies blood to the brain is blocked by a blood clot. A transient ischemic attack (TIA) or mini-stroke happens when blood flow to a part of the brain stops for a brief period of time. [9, 10]

According to the World Health Organization's Health Report, 15 million people suffer from stroke worldwide each year. Of these 5 million die and another 5 million become permanently disabled. In Europe, approximately 650,000 people die each year due to stroke. In UK, stroke is the third most common cause of death; and ischaemic stroke affects around 174-216 per 100,000 populations every year. [11, 12]

VI.2.2 Summary of treatment benefits

In stroke survivors, the recommended treatments for secondary stroke prevention include: risk factor modification, such as management of blood pressure, lipids, and glucose; quitting smoking; preventing clotting of blood in patients with atrial fibrillation (problem with irregular heart beat), stenting for patients with carotid stenosis (blockage and narrowing of the blood vessels supplying blood to the brain); and antiplatelet therapy (medicines that stop blood cells from sticking together and forming a blood clot). Presently, four antiplatelet therapy regimens have been approved for stroke prevention: single drug therapy with Aspirin, Ticlopidine, Clopidogrel, and the combination of Aspirin plus tablets releasing Dipyridamole slowly over a time period. All of these prevent formation of clots in the blood vessels that leads to inadequate blood flow to various organs. [13, 14]

One of the major studies showing the effectiveness of Dipyridamole in the prevention of secondary stroke and TIA was the second European Stroke Prevention Study (ESPS2). The patients were treated with sustained-release formulation of Dipyridamole alone (tablets releasing dipyridamole slowly over a time period), or low-dose aspirin alone, or the combination of both these medicines, for the prevention of secondary stroke and TIAs. The combined therapy with Dipyridamole and Aspirin resulted in more effective stroke prevention than treatment with either Aspirin alone or Dipyridamole alone. The combination therapy can also prevent the recurrence of TIA in patients with a previous history of TIA or stroke.

The results of ESPS2 study were supported by the results of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT study) that studied the effect of the combination therapy of Dipyridamole + Aspirin on the composite endpoint including stroke, death, myocardial infarction (heart attack) and/or severe bleeding. A risk reduction of 20% was observed for this composite endpoint with the combination therapy compared to Aspirin alone.

VI.2.3 Unknowns relating to treatment benefits

There is no information available regarding safety and effectiveness of Dipyridamole in children, and its impact on human fertility (ability to produce off-springs).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Intolerable headache	When the treatment with Dipyridamole is initiated, the patient may experience intolerable headache. Headache is a very common side-effect associated with the use of Dipyridamole, though it disappears with continued treatment. Thus, use of Dipyridamole may also have minor influence on the person's ability to drive and operate machines. Overdose (intake of the dose more than recommended one) of Dipyridamole may also lead to headache.	If the patient experiences intolerable headache in the beginning of the treatment with the medicinal product, change in dosage may be required. The recommend dosage is of one capsule at bedtime and a low dose of acetylsalicylic acid (pain-killer) in the morning. Once the headache disappears, normal dosage regimen should be started within a week, as the efficacy of this alternative dosing has not been established till now. If the patient is experiencing headache, he should be cautious while driving and operating machines. The patient may be given pain-killers for headache relief.
Use in patients with disorders related to heart and the blood vessels leading to poor blood to/from the heart (Use in patients with severe coronary artery disease, left ventricular outflow obstruction and haemodynamic instability)	Dipyridamole causes widening of the blood vessels (vasodilation), leading to decreased blood flow to the heart, and thus, may worsen the condition of the patients with following diseases: • Severe coronary artery disease (poor blood flow to the heart due to narrowing of blood vessels) which includes chest pain at rest (unstable angina) and recent heart attack (myocardial infarction) • Blockage of blood flow from the left lower heart chamber (left ventricular outflow obstruction) • Inability of the heart to pump blood (decompensated heart failure). Dipyridamole increases the concentration of adenosine (medicine for irregular heart-beats) in the blood, and thus, may increase the effect of the medicine on heart, leading to harmful	The medicinal product should not be used in patients with the disorders related to heart and the blood vessels leading to poor blood to/from the heart. Caution is necessary when combining the medicinal product with adenosine. The dosage of adenosine might need to be adjusted. The patients experiencing chest pain may be given other medicines to provide relief.

Risk	What is known	Preventability
	effects in the patients. Chest pain is a common side-effect of Dipyridamole, and has also been associated with its overdose.	
Simultaneous use with medicines used to treat high blood pressure, myasthenia gravis (weakness of muscles), blood clotting and asthma (Drug-drug interactions with antihypertensives [hypotension], cholinesterase inhibitors [reduced effect of cholinesterase inhibitors], anticoagulants and platelet inhibitors [potentiation of bleeding] and theophylline and other xanthines [reduces effect of dipyridamole])	Blood pressure is the force of the blood against the blood vessels as the heart pumps the blood. Dipyridamole leads to widening of the blood vessels, leading to decreased blood pressure. Thus, its simultaneous use with the medicines used to treat high blood pressure (antihypertensives) may add to the blood pressure lowering effect of these medicines. Myasthenia gravis is disease that causes weakness in the muscles under the control of the person. It happens because of a problem in communication between the nerves and muscles. Muscle weakness and pain is a common side-effect associated with the use of Dipyridamole. Thus, its simultaneous use may decrease the effect of the medicines used to treat myasthenia gravis (anticholinesterases), leading to further worsening of the disease. Use of Dipyridamole has been associated with increased risk of bleeding. Thus, its simultaneous use with other medicines that prevent blood clotting (anticoagulants and platelet inhibitors; e.g. warfarin, acetyl salicylic acid) can enhance the bleeding events, though it does not increase the occurrence of such events. Xanthenes like theophylline (medicines used to treat asthma i.e. difficulty in breathing) oppose the actions of Dipyridamole and thus, may lead to lowering of its effects, especially when xanthines are given via injection.	The medicinal product should be used with caution in patients taking medicines for high blood pressure, myasthenia gravis, blood clotting and asthma. The dosage of anticholinesterase (medicine to treat myasthenia gravis) might need to be adjusted in patients taking the medicinal product. The patients should be carefully monitored while receiving medicines to prevent blood clotting along with the medicinal product.
Dizziness	Dizziness (feeling sleepy) is a very common side-effect associated with the use of Dipyridamole and thus, may influence the person's ability to drive and use machines.	The patients taking the medicinal product should be cautious while driving and operating machines.

Risk	What is known	Preventability
	Dizziness can also occur with the overdose of Dipyridamole.	
Muscle pain (Myalgia)	Muscle pain is a common side-effect associated with the use of Dipyridamole.	If the patient experiences muscle pain, he should visit the physician, and adequate treatment should be initiated.

Important potential risks

Risk	What is known
Gallstones in elderly patients	Dipyridamole has been found in the gallstones in different amounts in few patients. These patients were all elderly, had evidence of ascending cholangitis (inflammation of the tract that carries bile), and had been treated with oral Dipyridamole for a number of years. However, no evidence is available to prove its role in initiation of the gall stones. It is possible that Dipyridamole might be incorporated in the gall stones during its metabolism in the body by bacteria. If the patient experiences any pain in the stomach area with the use of the medicinal product, he should visit physician or hospital as it could be due to gall bladders. The patient may require some immediate treatment.
Decreased blood platelets (Thrombocytopenia)	Thrombocytopenia is a condition characterised by lower than normal number of platelets (responsible for blood clotting and prevention of bleeding). It may occur with the use of Dipyridamole. Prolonged bleeding has also been noted with the overdose of Dipyridamole. Various studies have shown the increased risk of thrombocytopenia (including thrombocytopenic purpura, characterised by decreased platelets and purple bruising on the skin) along with increased bleeding, associated with the use of Dipyridamole. Thus, the patients taking the medicinal product should be regularly monitored. The patients may be given medicines to stop the bleeding.
Increased heart-beats (Tachycardia)	Increased heart-beats (tachycardia) have been observed with the use of Dipyridamole at normal and at doses higher than the recommended dose. Stress testing is a test performed to determine the function of heart during stress, like induced by exercise; and helps in diagnosis of various heart diseases like coronary heart disease and heart failure. Stress testing can be done using Dipyridamole in the patients who cannot exercise. Various studies have shown the increased risk of tachycardia with the use of Dipyridamole, especially during stress testing. The stress test may also give false results due to tachycardia induced by the

Risk	What is known
	medicinal product itself. Thus, the patients should be carefully monitored while taking the medicinal product. The patient may be given medicines to prevent tachycardia. The medicinal product should be withdrawn 24 hours early, if the stress test has to be performed using dipyridamole.

Missing information

Risk	What is known
Use in children	There is no information available regarding safety and effectiveness of Dipyridamole in children. Thus, use of the medicinal product is not recommended in children.
Effect on human's ability to reproduce (Impact on human fertility)	Animal studies have not revealed any effect of Dipyridamole on their ability to reproduce. In addition, no human studies have been done till now which shows the effect of Dipyridamole on human fertility.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Routine risk minimisation is provided through the SPC and the patient information leaflet (link to the product information). No additional risk minimisation measures are planned for this product.

VI.2.6 Planned post-authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

This is the first risk management plan for Dipyridamole Mercury(Dipyridamole) 200 mg Prolonged-Release Hard Capsules.