

PART VI SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY MEDICINAL PRODUCT

VI.1 Elements for summary tables in the European Public Assessment Report

VI.1.1 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> <input type="checkbox"/> Use in patients with low blood sodium levels (hyponatraemia) <input type="checkbox"/> Use in patients with low blood potassium levels (hypokalaemia) <input type="checkbox"/> Use in patients with kidney function disorder (renal dysfunction) <input type="checkbox"/> Use in patients with liver function disorder (hepatic dysfunction) <input type="checkbox"/> Use in patients with adrenal gland failure (suprarenal gland failure) <input type="checkbox"/> Use in patients with increased levels of chloride in blood (hyperchloraemic acidosis) <input type="checkbox"/> Long-term use in patients with chronic non-congestive angle-closure glaucoma <input type="checkbox"/> Use in patients allergic to sulphonamides (hypersensitive)
Important potential risks	<ul style="list-style-type: none"> <input type="checkbox"/> Suicidal ideation and behaviour <input type="checkbox"/> Risks associated with the administration of

Summary of safety concerns	
	<p>the drug product at an increased dose</p> <ul style="list-style-type: none"> □ Risks associated with long-term therapy □ Use in patients with lung disorders and breathing problems (pulmonary obstruction or emphysema) □ Use in patients with diabetes or those unable to breakdown glucose (impaired glucose tolerance)^a □ Death of the skin tissue (skin necrosis)^b
Important missing information	<ul style="list-style-type: none"> □ Use during pregnancy and breast-feeding (lactation)

^aPotential risk for acetazolamide 250 mg prolonged-release capsules

^bPotential risk for acetazolamide 500 mg powder for solution for injection

VI.1.2 Table of on-going and planned studies in the post-authorisation pharmacovigilance development plan

Not applicable

VI.1.3 Summary of post-authorisation efficacy development plan

Not applicable

VI.1.2 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Use in patients with low blood sodium levels (hyponatraemia)	The risks associated with the use of the medicinal product in patients with low blood levels are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with low blood potassium levels (hypokalaemia)	The risks associated with the use of the medicinal product in patients with low potassium levels are described in the SPC, and appropriate advice is provided to the prescriber to	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	minimise these risks.	
Use in patients with kidney function disorder (renal dysfunction)	The risks associated with the use of the medicinal product in patients with kidney function disorder are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with liver function disorder (hepatic dysfunction)	The risks associated with the use of the medicinal product in patients with liver function disorder are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with adrenal gland failure (suprarenal gland failure)	The risk associated with the use of the medicinal product in patients with adrenal gland failure is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with increased levels of chloride in blood (hyperchloraemic acidosis)	The risk associated with the use of the medicinal product in patients with increased levels of chloride in blood is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Long-term use in patients with chronic non-congestive angle-closure glaucoma	The risks associated with the long-term use of the medicinal product in patients with chronic non-congestive angle-closure glaucoma are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients allergic to sulphonamides (hypersensitive)	The risks associated with the use of the medicinal product in patients allergic to sulphonamides are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks		
Suicidal ideation and behaviour	The risk of developing suicidal thoughts associated with the use of the medicinal product is described in the SPC, and appropriate advice is provided to the prescriber to minimise this risk.	None
Risks associated with the administration of the drug product at an increased dose	The risks associated with administration of the drug product at an increased dose are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks	None
Risks associated with long-term therapy	The risks associated with long-term therapy with the medicinal product are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with lung disorders and breathing problems (pulmonary obstruction or emphysema)	The risks associated with the use of the medicinal product in patients with lung disorders and breathing problems are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with diabetes or those unable to breakdown glucose (impaired glucose tolerance) ^a	The risks associated with the use of the medicinal product in patients with diabetes or those unable to breakdown glucose are described in the SPC, and appropriate advice is provided to the prescriber to minimise these risks.	None
Death of the skin tissue (skin necrosis)	The risk of death of skin tissue associated with intravenous use of the drug product is described in the SPC, and appropriate advice is provided to the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	prescriber to minimise this risk	
Important missing information		
Use during pregnancy and lactation (breast-feeding)	The SPC provides no information regarding experience of the use of the drug product in pregnant and breast-feeding women, and suggests that the drug product should not be used in pregnancy, especially during the first trimester; and should be administered with great caution to lactating women	Not applicable

^aPotential risk for acetazolamide 250 mg prolonged-release capsules

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Glaucoma

Glaucoma is an eye condition where the nerve at the back of the eye (the optic nerve) is damaged. This can lead to loss of vision. In most cases, the damage to the optic nerve is due to an increased pressure within the eye (IOP).¹ Globally, 12.5 million people are blind from glaucoma. In the UK, it accounts for 10 out of 100 of registrations of blindness. Primary open-angle glaucoma (condition with no known cause and IOP greater than 21 mmHg) occurs in about 2% of people over 40 years, and 10% of these people are over 75 years of age. It accounts for a total of 480,000 affected individuals in England.²

Abnormal retention of fluids

Abnormal retention of fluids or oedema, also known as dropsy, is the medical term for fluid accumulation in the body. The build-up of fluid causes the affected tissue to become swollen. The swelling can occur in one particular part of the body or in the entire body.³

Congestive heart failure (CHF) is a very serious heart condition in which the heart cannot pump enough blood around the body at right pressure. As a result of CHF, fluid may collect in the lower legs, causing swelling, or in the lungs, causing shortness of breath. It is estimated that more than 23 million people worldwide have heart failure. In the USA, heart failure affects nearly 5.8 million people of all ages and is responsible for more hospitalisations than all forms of cancer combined. Approximately 670,000 new cases of heart failure are diagnosed each year in the USA. About 277,000 deaths are caused by heart failure each year. Heart failure accounts for 34% of heart-related deaths. The number of heart failure cases diagnosed in men and women are similar and increases with age. Heart failure occurs in 2% of the population younger than 55 years and increases to 10% for persons older than 75 years.^{4,5}

Oedema is the term for fluid retention. Oedema can be caused by various conditions, especially diseases of the heart or kidney. Peripheral oedema is the swelling of tissues, usually in the lower limbs, due to the accumulation of fluids. Some of the drugs are also responsible for increasing the fluid pressure from sodium and water retention such as calcium antagonists, non-steroidal anti-inflammatory drugs, insulin and prolonged steroid therapy.⁶

Epilepsy

An epileptic seizure (fit) is the transient occurrence of signs or symptoms due to abnormal electrical activity in the brain, leading to a disturbance of consciousness, behaviour, emotion and sensation. Epilepsy most commonly starts in children or in people older than 60 years of age. After childhood, the occurrence of epilepsy increases with age. In the UK, the frequency of occurrence of epilepsy is estimated to be 50 per 100,000 per year, and the number of active epilepsy is estimated to be 5–10 cases per 1,000. In a study conducted in the UK, it is estimated that in people aged over 60 years, 11.8 cases per 1,000 suffer from epilepsy, and the overall annual occurrence in those over 60 years was estimated to be 117 per 100,000.⁷⁻⁹

VI.2.2 Summary of treatment benefits

Acetazolamide is a weak diuretic (drug which promotes the production of urine and treat high pressure) and is mainly used in the management of glaucoma. As a diuretic, it stops the action of the enzyme carbonic anhydrase. As a result, the amount of some salts in the body is reduced and this promotes the loss of fluid from the body.

Glaucoma

Many clinical studies have shown the effectiveness of acetazolamide in the treatment of glaucoma. Some recent studies have reported that acetazolamide 250 mg tablets given twice daily can control the IOP adequately.

A study in patients with open-angle glaucoma (a type of glaucoma) concluded that the condition of most patients was controlled by a single night-time dose of acetazolamide administered orally as 500 mg tablets or modified-release capsules.

A small clinical study was conducted to check the efficacy of acetazolamide 250 mg or 500 mg sustained release capsules in open-angle glaucoma patients with uncontrolled IOP. The sustained release capsules of acetazolamide were reported to decrease the level of IOP by 5–8 mmHg at 250 mg dose and 5–9 mmHg at 500 mg dose.

Epilepsy

Acetazolamide has also been found to be effective in various types of epilepsy. Some studies have reported beneficial effects of acetazolamide in combination with carbamazepine (another anti-epileptic drug) in patients suffering from partial seizures (affecting only part of the brain at the onset of seizure, and not responding to other treatments for epilepsy). The major drawback to the long-term use of acetazolamide is the development of tolerance, but this may be prevented or delayed by using it in conjunction with other anti-epileptics. Acetazolamide has been shown to have greater activity in children than in adults.

VI.2.3 Unknowns relating to treatment benefits

Limited information is available on the use of acetazolamide in pregnant and breast-feeding women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in patients with low blood sodium levels (hyponatraemia)	<p>Carbonic anhydrase is one of the enzymes found in the body, which carry out fast interconversion of carbon dioxide and water to bicarbonate ions and protons. In the kidney, hydrogen ions normally combine with filtered bicarbonate ions in the urine, to form carbonic acid. Carbonic acid in turn is normally acted upon by carbonic anhydrase, leading to formation of carbon dioxide. As carbon dioxide leaves from the kidney, more bicarbonate ions are reabsorbed in the kidney.</p> <p>Acetazolamide stops the activity of the enzyme, thus causing an increase in level of carbonic acid. Subsequently, bicarbonate is not reabsorbed by the body and is removed in the urine along with sodium and potassium. The use of this medicinal product in patients with hyponatraemia can further decrease their body's sodium level and worsen their condition.</p>	<p>Yes, acetazolamide should not be used in patients with hyponatraemia. Before administration of the medicinal product, the electrolyte levels should be checked.</p> <p>Caution is also necessary while prescribing the prolonged-release preparation to patients who are associated with, or are at risk of, developing electrolyte imbalances, such as those with reduced kidney function (including elderly patients), lung disorders, breathing problems and diabetes mellitus. In addition, periodic monitoring of electrolyte levels is required, even in patients with normal renal function being treated with the prolonged-release preparation of this medicine.</p>
Use in patients with low blood potassium levels (hypokalaemia)	<p>Acetazolamide stops the activity of the enzyme carbonic anhydrase, thus causing an increase in the level of carbonic acid. Subsequently, bicarbonate is not reabsorbed by the body and is removed in the urine along with sodium and potassium. The use of this medicinal product in patients with hypokalaemia can further decrease their body's potassium level and worsen their condition.</p>	<p>Yes, acetazolamide should not be used in patients with hypokalaemia. Before administration of the medicinal product, the electrolyte levels should be checked.</p>
Use in patients with kidney function disorder (renal dysfunction)	<p>Acetazolamide is associated with causing kidney stones, and therefore not to be used in patients suffering from kidney function disorder.</p>	<p>Yes, acetazolamide should not be used in patients with kidney function disorder.</p> <p>Patients who have or ever had kidney stones should only use the medicinal</p>

Risk	What is known	Preventability
		product, if the benefit from its use outweighs the risk of further aggravating the condition.
Use in patients with liver function disorder (hepatic dysfunction)	<p>Acetazolamide must not be used in patients suffering from liver function disorder.</p> <p>Hepatic cirrhosis is an abnormal liver condition in which normal liver cells are damaged and are then replaced by scar tissues. Patients with hepatic cirrhosis should not use the medicinal product as it may increase the risk of hepatic encephalopathy. Hepatic encephalopathy occurs as a result of liver failure, in which abnormal functioning of brain occurs when the liver is unable to remove harmful substances in the blood.</p> <p>In addition, few patients of hepatic cirrhosis in whom fluid accumulation had occurred may experience disorientation and lose the sense of time, direction and recognition of people. Close supervision of these subjects is required when treated with this medicinal product.</p>	Yes, acetazolamide should not be used in patients with liver function disorder.
Use in patients with adrenal gland failure (suprarenal gland failure)	<p>Adrenal glands are located above the kidney and produce certain hormones which are responsible for sodium conservation, potassium secretion and water retention in the body.</p> <p>Patients with adrenal gland failure are unable to produce those hormones, causing weakness, dizziness and darkening of skin. Administration of acetazolamide to such patients can worsen their condition.</p>	Yes, acetazolamide should not be given to patients with adrenal gland failure as it can worsen their condition.
Use in patients with increased levels of chloride in blood (hyperchloremic	Acidosis is a condition in which there is too much acid in the	Yes, acetazolamide should not be given in cases of

Risk	What is known	Preventability
acidosis)	body. When kidneys are unable to remove enough acid from the body, it is called metabolic acidosis. Acetazolamide causes loss of bicarbonate (along with sodium) through the kidney, and increase in blood chloride levels, thus causing hyperchloremic metabolic acidosis.	hyperchloremic acidosis
Long-term use in patients with chronic non-congestive angle-closure glaucoma	<p>Glaucoma is an eye disease in which the pressure inside the eye slowly increases causing damage to the eye nerve. Non-congestive angle-closure glaucoma is the condition in which the pressure in the front chamber of the eye increases due to slow progressive blockage of the normal circulation of fluid within the eye.</p> <p>Acetazolamide reduces the production of fluid inside the eye which in turn reduces the build-up of pressure in the eye (IOP). However, in cases of chronic non-congestive angle-closure glaucoma, treatment with this medicine may further aggravate the condition.</p>	Yes, this product should not be used in patients with chronic non-congestive angle-closure glaucoma.
Use in patients allergic to sulphonamides (hypersensitive)	Acetazolamide belongs to the chemical class of drugs called sulphonamides. People who are allergic to sulphonamides may experience shortness of breath, swelling of the eyelids, face or lips, rash or itching (especially affecting whole body) upon administration of this medicine.	<p>Yes, acetazolamide should not be given to the patients allergic to sulphonamides.</p> <p>Any kind of allergic reaction should be reported to the doctor immediately.</p> <p>If any serious life-threatening event occurs, then the treatment with this medicine needs to be immediately stopped such as in the case of marked decrease of the blood cells or appearance of toxic skin reactions.</p>

Important potential risks

Risk	What is known
Suicidal ideation and behaviour	A small number of people being treated with acetazolamide for epilepsy (fits) have reported of having thoughts of harming or killing themselves. The patients and caretakers of the patients are advised to contact their doctor immediately if signs of suicidal ideation or behaviour are observed.
Risks associated with the administration of the drug product at an increased dose	<p>Increasing the dose does not increase effectiveness of the medicinal product; however, it may increase the risk of drowsiness or paraesthesia (sensation of tickling or numbness). In addition, dizziness, tiredness and ataxia (lack of voluntary coordination of muscle movements) may also develop.</p> <p>Increasing the dose may sometimes result in the decreased desired effect on the urine production. In some situations, very large doses of this medicine is combined with other diuretics to secure diuresis (increase in the production of urine by the kidneys), such as in conditions of complete failure.</p>
Risks associated with long-term therapy	<p>The medicinal product should be used with great caution when used for a long duration. If taken for a long time, it can occasionally affect the amount of bicarbonates, potassium or sodium in the blood. This can further change the pH of the blood and can lead to too much of acid production in the body (metabolic acidosis) due to loss of bicarbonates. Patients experiencing such problem are usually given preparations containing bicarbonates to maintain the electrolyte balance in the body.</p> <p>Few cases of unusual skin rashes have also been reported on long-term use of the medicine.</p>
Use in patients with lung disorders and breathing problems (pulmonary obstruction or emphysema)	Acetazolamide may increase the acidity of the blood in patients suffering from breathing problems or lung disorders, such as pulmonary obstruction or emphysema (lung disease with damage to air sacs in the lungs). In these patients, the breathing pattern is already impaired; therefore, the medicine should be used with caution as it can further aggravate the condition.
Use in patients with diabetes or those unable to breakdown glucose (impaired glucose tolerance)	In impaired glucose tolerance, blood glucose levels are higher than normal, but are not high enough to cause diabetes. This medicine should be administered with caution to patients with impaired glucose tolerance or diabetes, as it can cause an increase as well as decrease in blood glucose levels.
Death of the skin tissue (skin necrosis)	Care needs to be taken while administering acetazolamide via intravenous route to avoid any leakage of the medicinal product due to ruptured blood vessels which could lead to skin necrosis.

Important missing information

Risk	What is known
Use during pregnancy and breast-feeding (lactation)	According to the animal studies, acetazolamide has been reported of causing birth defects and toxic effects to embryo. However, there is no information on these effects in human beings. Therefore, acetazolamide should not be used in pregnant woman, especially during the first three months. Acetazolamide has been found in low quantity in the milk of lactating women. It is unknown if the medicinal product can cause harm to the nursing babies; caution should be exercised when prescribing the medicine to nursing mothers. Breast-feeding is not recommended during treatment with this medicinal product.

VI.2.5 Summary of 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 acetazolamide 250 mg tablets, 250 mg prolonged-release capsules and 500 mg powder for solution for injection.