

SUMMARY OF THE RISK MANAGEMENT PLAN FOR ZONISAMIDE MYLAN (ZONISAMIDE)

Overview of disease epidemiology

Zonisamide is an anti-epileptic which is indicated for the treatment of partial seizures with or without secondary generalisation in adults with newly diagnosed epilepsy or as an adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents and children aged 6 years and above.

Epilepsy is a chronic disorder that affects people of all ages all around the world, it is estimated that around 50 million people in the world have epilepsy, however being more predominant in developing countries where the estimated proportion of the general population with active epilepsy is between 6 to 10 per 1000 in comparison to 4 to 10 per 1000 in non-developing countries. Unfortunately in developing country three fourths of the affected people do not get the treatment they require. The risk of premature death in people with epilepsy is two or three times higher than it is for general population.

Summary of treatment benefits

Zonisamide is used as an anti-epileptic medicine. Zonisamide is used to treat seizures that affect one part of the brain which is known as a partial seizure, which may or may not be followed by a seizure affecting all of the brain which is known as secondary generalisation. The medicinal product can be used on its own to treat seizures in adults or with other similar medications to treat seizures in adults, adolescents and children aged 6 years and above.

Studies have been performed to confirm the efficacy of zonisamide to treat seizures that affect one part of the brain with or without a seizure affecting all of the brain. The study was performed in 583 adults who had recently been diagnosed with partial seizures with or without seizures affecting all of the brain. The consisted of treatment with zonisamide in comparison to another known anti-epileptic drug called carbamazepine. The adult subjects at random were either given zonisamide or carbamazepine for a course of 24 months.

Overall, 79.4% of patients treated with zonisamide compared to 83.7% patients treated with carbamazepine were seizure- free for more than 26 weeks.

Furthermore, as an add on therapy with other similar medications to treat seizures in adults, adolescents and children aged 6 years and above, zonisamide has shown positive efficacy of in many studies, resulting in a median decrease in seizures affecting one part of the brain at doses of 300-500mg per day.

These studies were conducted for innovator product by Innovator Company and not by Mylan.

Unknowns relating to treatment benefits

The use of zonisamide has not been studied adequately in patients with liver impairments and in paediatric patients below the age of 6. As the safety and efficacy of zonisamide has not been established in these special populations caution should be taken when being treated. Furthermore, as for now routine Pharmacovigilance activities are sufficient to monitor these risks.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic Reaction (hypersensitivity)	Allergic reactions, including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing (which requires treatment right away).	Prescribers should be aware if the patient has previously experienced hypersensitivity reactions and should instruct the patient to inform them about the early symptoms. Furthermore, prescriber should make patient aware if they know of any known allergy to the ingredients within zonisamide.
Skin reactions (skin eruptions)	Serious skin reactions can occur with zonisamide use, which can be minor in presentation or severe such as Steven Johnsons Syndrome.	Prescribers should be aware if the patient has previously experienced skin reactions and should instruct the patient to inform them about the early symptoms so treatment can be discontinued accordingly.

Risk	What is known	Preventability
Blood disorders, (Hematologic events)	Can cause decrease in white blood cell counts and in platelets which can increase your bleeding time.	Prescriber should make patients aware of such conditions that occur with zonisamide use and monitor them to ensure a decrease in such blood counts do not occur.
Kidney stones	Kidney stones can be very painful and can obstruct kidney function and in worst case scenarios if left untreated can lead to kidney failure.	Prescribers should make patients aware of kidney stones with zonisamide use and instruct them to inform them if they have any form of pain or symptoms related to kidney stones to avoid any profound effects.
Fluctuations in body temperature and dehydration (disordered body temperature (oligohydrosis and hyperthermia) and dehydration.	Zonisamide use can cause an increase in patient's body temperature especially in heated climates which could lead to having a heat stroke. Especially in the paediatric population.	Prescribers should make patients well aware that zonisamide use can cause fluctuations in a patient's temperature and a number of precautions should be taken, prescribers should instruct patients with what cautions should be taken such as drinking water and staying in shaded places.
Pancreatitis and elevated amylase and lipase.	Pancreatitis is scientific term of an inflamed pancreas which is an important organ of the digestive system. Pancreatitis can lead to decrease pancreas function	Prescribers should make patients aware of the signs and symptoms associated with pancreatitis and instruct them to inform them if they experience any of these

Risk	What is known	Preventability
	<p>leading to other digestive problems. Furthermore, it can be painful for the patients and if left untreated could be fatal.</p>	<p>symptoms as immediate care should be taken.</p>
Muscle disorders	<p>Muscle problems such as unexplained muscle pain, tenderness, or weakness may occur during treatment. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy, however, if undiagnosed, they may evolve and cause kidney problems.</p>	<p>Prescribers should be aware if patients has previously encountered any muscle problems before and make them aware of symptoms and that zonisamide can cause such effects and that they should instruct the doctor if such symptoms occur as zonisamide therapy may need to be discontinued.</p>
Weight loss	<p>Zonisamide is known to cause some weight loss.</p>	<p>Prescribers should make patients aware that weight loss can occur with zonisamide use furthermore patients should be monitored and should be instructed on what actions are to be taken if weight loss occurs.</p>
Metabolic acidosis and its potential for osteopenia	<p>Metabolic acidosis can lead to problems in development and maturation due to possible decrease in bone health.</p>	<p>Prescribers should make patients are of the risk and what precautions and actions should be taken if such symptoms relating to metabolic acidosis occur, Furthermore, paediatric patients should be closely</p>

Risk	What is known	Preventability
		monitored as it can have profound effects on development.
Suicide thoughts/suicide.	Suicidal thoughts and suicide is a known adverse event of zonisamide.	Prescribers should be aware of patient's medical history (e.g. behavioural disorders or depression) and concomitant medicinal intake which could put them at risk of experiencing suicidal thoughts, furthermore carers of patients receiving zonisamide should also be made aware of this risk. If such thoughts are observed, patient should immediately seek medical attention as therapy with zonisamide may need to be discontinued.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizures following sudden withdrawal	Seizures have been observed in patients who suddenly abrupt therapy with zonisamide. It is advised that zonisamide therapy should be discontinued gradually.
Effects on ability to drive and use machines	Zonisamide is known to cause side effects such as dizziness, confusions and somnolence therefore it is advised that caution should be taken when operating machinery, driving or performing any activity which requires alertness and attention to avoid any accidents from occurring.

Risk	What is known (Including reason why it is considered a potential risk)
Use in renal impairment	It has been identified that zonisamide can have some nephrotoxic effects such as kidney stones furthermore studies have shown that there is a positive correlation between plasma AUC of zonisamide with creatinine clearance. Therefore caution should be taken when prescribing doses to renal impaired patients.
Pregnancy issues.	As per studies there is no strong correlation that zonisamide can have toxic effects during pregnancy or on the fetus. However, toxic effects have been observed in animal studies, potential risk to humans is unknown. Therefore, zonisamide use in pregnancy is contraindicated and only should be used if the physician feels that the potential benefit of zonisamide use is considered to justify the risk to the fetus.
Use in elderly.	Generally elderly people have reduced kidney function and zonisamide is primarily digested through the kidneys therefore caution should be taken when prescribing its use within this population. Furthermore, some adverse events have been observed at a higher incidence rate in the elderly population such as skin rash (pruritus).
Developmental and maturational impairment in children and adolescents	It is known that zonisamide can cause weight loss which can have profound effects on growth and development in the young. Patients should be closely monitored for risk of weight loss and a dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts, otherwise zonisamide should be discontinued.

Missing information

Risk	What is known
Use in impaired liver function	The safety and use of zonisamide in patients with impaired liver function has not been adequately studied. Therefore

Risk	What is known
	caution should be taken in such patients and closely monitored.
Use in children below 6 years.	The safety and use of zonisamide in children below 6 years has not been adequately studied. Therefore caution should be taken in such patients and closely monitored.

Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. The measures in these documents are known as routine risk minimisation measures.

Planned post authorisation development plan

No studies planned.

Summary of changes to the Risk Management Plan over time

Version 1 has been updated to version 2 in line with CHMP day 120 list of questions for Zonisamide 25 mg, 50 mg and 100 mg hard capsules, procedure number EMEA/H/C/004127. Information in the section of V.1 and VI.2.4 for the risk of “developmental and maturational impairment in children and adolescents” is updated.

This summary was last updated in Jan-2016.