VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Epilepsy is a chronic brain disorder that affects people of all ages. It is characterized by recurrent brief episodes of involuntary shaking (seizures) which may involve a part of the body (partial) or the entire body (generalized) and sometimes accompanied by loss of consciousness and control of bowel or bladder function. The episodes are a result of excessive electrical discharges in a group of brain cells. Seizures can vary from the briefest lapses of attention or muscle jerks, to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day.

The estimated proportion of the general population with active epilepsy is between 4 to 10 per 1,000 people (in developing countries between 6 to 10 per 1,000). Around 50 million people in the world have epilepsy; nearly 80 % are found in developing regions (WHO 2014).

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience, zonisamide represents an effective drug in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy as well as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above. If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, zonisamide can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Since only limited data are available Zonisamide is not recommended for use in:

- children <6 years of age

- patients with impaired liver function

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reaction (Hypersensitivity)	Zonisamide belongs to a group of medicines (sulphonamides) which can cause severe allergic reactions which very rarely can be fatal. An allergic reaction may occur in people who are allergic to zonisamide, other sulphonamide medicines (e.g. sulphonamide antibiotics, thiazide diuretics and sulfonylurea antidiabetes medicines) or any of the ingredients in this medicine (listed in section 6 of PIL)	Patients should contact their doctor immediately if they have difficulty breathing, a swollen face, lips or tongue, or a severe skin rash as these symptoms may indicate that they are having a severe allergic reaction.
Unexplained rash	Serious rashes have occurred in association with zonisamide therapy, including isolated cases of Stevens-Johnson syndrome (reaction to a medication with painful red or purplish rash and skin peeling). Consideration must be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking zonisamide must be closely supervised, with additional levels of caution applied to those patients receiving other antiepileptic medicines that may independently induce skin rashes.	Patients should contact their doctor if they have an unexplained skin rash, as this could develop into a more severe skin rash or skin peeling. Doctor may decide that the patient stops using zonisamide.
Blood disorders (Hematologic events)	Isolated cases of agranulocytosis (lowered white blood cell count- most commonly of neutrophils), thrombocytopenia (lowered platelet count), leukopenia	If patients feel unusually tired or feverish, have a sore throat, swollen glands, or find that they bruise more easily, they should contact their doctor as this may mean they have a blood

Risk	What is known	Preventability
	(lowered white blood cell count), aplastic anaemia (disease of the bone marrow), pancytopenia (deficiency of all three blood cell types) and leucocytosis (increase in white blood cell count) have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.	disorder. Doctor may decide that the patient stops using zonisamide.
Kidney stones	Among 991 patients treated with zonisamide during its development, 40 patients (4.0%) with epilepsy receiving developed clinically possible or confirmed kidney stones. Zonisamide should also be used carefully in adults when taken with medicines that can cause kidney stones, like topiramate or acetazolamide. In children, this combination is not recommended.	Patients should tell their doctor or pharmacist before taking zonisamide if they have previously suffered from kidney stones, as they may be at increased risk of developing more kidney stones. They can reduce the risk of kidney stones by drinking sufficient water. Patients should also inform their doctors if they get a sudden pain in their back or stomach, have pain on urinating (passing water) or notice blood in their urine, as this may be a sign of kidney stones.
Heat stroke and dehydration	Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric. Caution should be used in patients when zonisamide is prescribed with other medicinal products that can cause heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity. Heat stroke requiring hospital treatment was diagnosed in some cases. Heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. Physicians should discuss with	Patients should talk to their doctor or pharmacist before taking Zonisamide if they are younger than 12 years, as they may be at greater risk of decreased sweating and heat stroke. Doctors should also be informed in case patients live in a place or are on holiday in a place where the weather is warm. Zonisamide can make you perspire less, which can cause your body temperature to increase. Reduce the risk of overheating by drinking sufficient water and keeping cool. Zonisamide can cause your child to sweat less and overheat and if your child is not treated this can lead to

Risk	What is known	Preventability
	patients and their carers the potential seriousness of heatstroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms.	brain damage and death. Children are most at risk especially in hot weather. Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke. When your child is taking zonisamide: • Keep your child cool especially in hot weather • Your child must avoid heavy exercise especially when the weather is hot • Give your child plenty of cold water to drink • Your child must not take these medicines: carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin). If your child's skin feels very hot with little or no sweating, becomes confused, has muscle cramps, or your child's heartbeat or breathing becomes rapid: • Take your child to a cool, shaded place • Sponge your child's skin with cool (not cold) water • Give your child cold water to drink • Seek urgent medical assistance. In the event of signs or symptoms of dehydration,

Risk	What is known	Preventability
		oligohydrosis, or elevated body temperature, discontinuation of zonisamide should be considered.
Inflamed pancreas (Pancreatitis and elevated amylase and lipase)	Pancreatitis (inflamed pancreas) may occur under treatment with zonisamide. The patients may experience severe upper abdominal pain which spreads to the back, nausea, vomiting.	In patients taking zonisamide who develop the clinical signs and symptoms of pancreas inflammation, it is recommended that pancreatic lipase and amylase levels (specific proteins in the blood) are monitored. If inflammation is evident, in the absence of another obvious cause, it is recommended that discontinuation of zonisamide be considered and appropriate treatment initiated.
Abnormal muscle breakdown which can lead to kidney problems (Rhabdomyolysis)	People taking zonisamide have experienced unexplained muscle pain, tenderness, or weakness. This is because on rare occasions, muscle problems, including muscle breakdown resulting in kidney damage, can occur and may become a potentially life-threatening condition.	If patients experience muscle pain or a feeling of weakness, they must inform their doctor as this may be a sign of abnormal muscle breakdown which can lead to kidney problems.
Weight loss	Zonisamide can cause weight loss. It should be used with caution if patients who are underweight, or have lost a lot of weight. Doctor should be consulted as this may need to be monitored.	If any of these applies, patients must tell their doctor before they take Zonisamide, as this may need to be monitored. This especially applies to children. You should monitor your child's weight every month and see your doctor as soon as possible if your child is not gaining enough weight. Zonisamide is not recommended for children who are underweight or have a small appetite, and should be used with caution in those below 20 kg.
Increased acid level in the blood (Metabolic acidosis)	Increased acid levels in the blood occur very rarely with	Patients should contact their doctor if they have signs of

Risk	What is known	Preventability
	zonisamide. The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in younger patients.	increased acid level in the blood-headaches, drowsiness, and shortness of breath and loss of appetite. Doctor may need to monitor or treat this. If metabolic acidosis develops and persists, the doctor should consider reducing the dose or gradually stopping Zonisamide therapy. Parents can reduce these risks by ensuring that their child drinks enough water and is not taking any other medicine which could cause a shift in blood acid level. Doctor should monitor child's blood bicarbonate levels and kidneys.
Thoughts or attempts of harming or killing yourself (Suicide ideation and behaviour)	Antiepileptic drugs, including zonisamide, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any antiepileptic drug for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour. The patients may experience: talking or thinking about wanting to hurt themselves or end their life, becoming preoccupied with death and dying, becoming depressed or having the depression get worse, withdrawing from friends and family.	Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizures following sudden withdrawal	In accordance with current clinical practice, discontinuation of zonisamide in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of other antiepileptic medicines (used at the same time) once seizure control with zonisamide has been achieved in the add-on situation, in order to reach monotherapy with zonisamide. Therefore, withdrawal of other anti-epileptic drugs used at the same time must be undertaken with caution. If the doctor advises you to stop taking zonisamide your dose will be reduced gradually to lower the risk of more seizures.
Effects on ability to drive and use machines	Zonisamide may affect your concentration, ability to react/respond, and may make you feel sleepy, particularly at the beginning of your treatment or after your dose is increased. Patients must be especially careful while driving or operating machinery, if zonisamide affects them in this way.
Use in renal impairment	Patients should inform their doctor or pharmacist before taking zonisamide if they suffer from kidney problems as the dose of zonisamide may need adjusting. Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients. Since zonisamide is excreted through kidneys, it should be discontinued in patients whose kidneys are not working properly or where a clinically significant increase in creatinine (protein in blood which signifies kidney health) is observed. Also, it is known that some people respond to lower doses. The dose may be increased more slowly if patient suffer from kidney problems
Hepatic dysfunction in paediatric and adolescent patients	Increased levels liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and bilirubin have occurred in paediatric and adolescent patients. If a liver problem is suspected, liver function should be evaluated by a doctor and stopping zonisamide therapy should be considered.
Use in the elderly	Patients should consult with their doctor or pharmacist before taking zonisamide if they are elderly, as the dose of zonisamide may need adjusting, and they may be more likely to develop an allergic reaction, severe skin rash, swelling of the feet and legs, and itchiness. It is also known that some people respond to lower doses. The dose may be increased more slowly if patients are elderly.

Risk	What is known (Including reason why it is considered a potential risk)
Disordered mental abilities and processes in patients younger than 18 years of age (Cognitive impairment in paediatric and adolescent patients)	Cognitive impairment in patients affected by epilepsy has been associated with already existing brain disorders and/or the administration of anti-epileptic treatment. A study has shown that the number of patients with disorders in mental abilities and processes was greater in patients who took zonisamide compared with the placebo group.
Use in pregnancy and breast-feeding	If a patient is pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, they should ask their doctor for advice before taking this medicine. Women of childbearing age must use adequate contraception while taking and for one month after stopping zonisamide. Women should take zonisamide during your pregnancy only if their doctor advises them to. Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. It also not advisable to breastfeed whilst taking, or for one month after stopping zonisamide. Zonisamide was teratogenic in multiple animal species, and can pass into breast milk. There are no clinical data available on the effects of zonisamide on human fertility.

Missing information

Risk	What is known
Use in impaired liver function	Patients should inform their doctor or pharmacist before taking zonisamide if they suffer from liver problems, as the dose of zonisamide may need adjusting. Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe liver impairment is not recommended. Caution must be exercised in treating patients with mild to moderate liver impairment.
Use in children below 6 years of age	For patients younger than 6 years old, zonisamide is not recommended because the safety and efficacy of zonisamide in that age group have not yet been established.

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.

The SmPC and the package leaflet are part of the medicine's product information.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

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

Not applicable