VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Zonisamide is used for the treatment of certain types of epilepsy (seizures). Epilepsies are among the most common nervous system disorders affecting individuals of all ages. Seizures and epilepsy affect children more than any other age group and are approximately twice as common in children as in adults (about 700 per 100,000 in children less than 16 years compared with 330 per 100,000 in adults). Partial epilepsies (focal or localization related) are frequent, accounting for more than 60% of all epilepsies.

VI.2.2 Summary of treatment benefits

The main benefit of treatments for epilepsy is to reduce the rate at which seizures (fits) occur with the aim of eliminating seizure occurrence completely. By reducing seizure occurrence, a patient's quality of life including every day activities and social acceptance are also likely to improve. A small number of patients may develop prolonged seizures (status epilepticus) which can lead to early death. An additional benefit of effective treatment is to reduce the risk of this condition developing.

There are many anticonvulsant medications available for the treatment of epilepsy including phenobarbital and phenytoin which have been available since the early 1900s and primidone, ethosuximide, carbamazepine and valproic acid/sodium valproate all of which can be regarded as first-generation antiepileptic drugs. More recently a number of additional medications have been developed which include vigabatrin, zonisamide, oxcarbazepine, lamotrigine, felbamate, gabapentin, topiramate, tiagabine, levetiracetam, pregabalin and lacosamide.

No single drug is effective in all patients with epilepsy. Around 60% of patients with newly diagnosed epilepsy will respond to treatment with one medication (monotherapy) without developing intolerable adverse effects. The remaining 30 to 40% will have epilepsy that is difficult to control from the start, although some of these patients will respond to a combination of medications. For a small minority of patients difficult to control epilepsy, neurosurgery may be a treatment option.

Zonisamide 25 mg, 50 mg and 100 mg is a generic version of Zonegran. The beneifits of zonisamide both as monotherapy and as an add-on adjunctive therapy have been demonstrated for the innovator product Zonegran. As Zonisamide is essentially similar to Zonegran, these benefits in seizure control apply equaly to Zonisamide 25 mg, 50 mg and 100 mg.

VI.2.3 Unknowns relating to treatment benefits

The effects of zonisamide have not been studied in young children, less than 6 years of age.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions *[Hypersensitivity reactions]*	Zonisamide contains a chemical structure known to be associated with allergic reactions (sulphonamide group). Allergic reactions have been reported commonly, which on very rare occasions can be serious.	Zonisamide should not be used in patients who are known to be allergic to the active substance, to other components in the capsules or who are known to be allergic to sulphonamides.
Serious and severe skin eruptions *[Serious and severe skin reactions, including Steven's Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)]*	Serious and severe skin eruptions with blistering and skin loss are a particular type of allergic reaction which has occurred very rarely with zonisamide.	Consideration should be given to stopping zonisamide in patients who develop unexplained skin rashes.
Effects on red and white blood cells and blood clotting elements *[Haematologic events]*	Cases of severe reductions in red and white blood cells and those cells involved in blood clotting (platelets) very rarely.	Blood cells should be monitored and consideration should be given to stopping zonisamide in patients who show reduced cell counts.
Kidney stones *[Renal stone formation]*	Some patients may be at increased risk for renal stones and associated signs and symptoms such as kidney pain. Kidney stones may lead to chronic kidney damage. Risk factors include prior stone formation, a family history of kidney stones and increased urine calcium. None of these risk factors can reliably predict stone formation during zonisamide treatment. In addition, patients taking other medications associated with kidney stones may be at increased risk.	Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

Risk	What is known	Preventability
Heat stroke *[Heat stroke (oligohidrosis, hyperthermia and dehydration)]*	Cases of decreased sweating and increased body temperature have been reported mainly in children. If not treated this may lead to brain damage.	Caution should be used in adults when zonisamide is prescribed with other medicinal products that predispose patients to heat related disorders; these include certain types of diuretics (called carbonic anhydrase inhibitors) and medicines that affect the nervous system control of sweating. Children in particular should be kept cool in hot weather, avoid exercise and drink plenty of cold water.
Severe inflammation of the pancreas *[Pancreatitis]*	Inflammation of the pancreas associated with severe pain has been reported very rarely with zonisamide.	Consideration should be given to stopping zonisamide in patients who develop abdominal pain and chemical changes suggesting pancreatic inflammation.
Destruction of muscle tissue *[Rhabdomyolysis]*	Muscle damage and chemical changes associated with muscle damage have been reported very rarely with zonisamide.	Consideration should be given to stopping zonisamide in patients who develop muscle pain and chemical changes suggesting muscle damage and where other causes (such as seizures or physical injury have been excluded).
Weight loss	Zonisamide commonly may cause weight loss. This is potentially more serious in children treated with zonisamide.	Dietary supplements or increased food intake may be considered if a patient is losing weight or is underweight whilst taking zonisamide. If substantial undesirable weight loss occurs, consideration should be given to stopping zonisamide.

Risk	What is known	Preventability
Metabolic and body chemical disturbance leading to bone thinning *[Hyperchloraemic, non-anion gap metabolic acidosis and potential for osteopenia]*	Chemical changes leading to increased acidity in body fluids and tissues (acidosis) is associated with zonisamide treatment due to its effect on the kidney. Generally this happens early in treatment, but can occur at any time during treatment. This effect appears to happen more often and is more sever in younger patients. If prolonged, this effect can affect bone strength.	If acidosis develops and persists, consideration should be given to reducing the dose or discontinuing zonisamide. If the decision is made to continue patients on zonisamide, alkali treatment should be considered to reduce the risk of effects on the body.
Thoughts about and pre-occupation with suicide, and suicidal behaviour *[Suicidal ideation and behaviour]*	Suicidal thoughts and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A analysis of many clinical studies of anti-epileptic medicines has also shown a small increased risk of suicidal thoughts and behaviour. How this happens is not known and the available information does not exclude the possibility of an increased risk for zonisamide.	Patients should be monitored for signs of suicidal thoughts or behaviour. Patients and carers should be advised to seek medical advice should signs of suicidal thoughts or behaviour emerge.

Important potential risks

Risk	What is known
Occurrence of fits (seizures) on drug withdrawal *[Withdrawal seizures]*	Stopping zonisamide suddenly may potentially cause seizures. When stopping treatment, it should be gradually reduced over a number of weeks.
Effects on ability to drive and use machines	Zonisamide may cause drowsiness and difficulty in concentration and as such patients should exercise caution during activities that require a high degree of alertness.
Use in patients with poor kidney function *[Use in patients with renal impairment]*	Zonisamide and its break-down products are removed from the body through the kidney. There is limited information of use in patients with poorly functioning kidneys and as such slower increases in dose may be needed to reach an effective dose. In patients who develop poor kidney function whilst on treatment with zonisamide, consideration should be given to stopping treatment

Use during pregnancy	There are no adequate information from the use of zonisamide in pregnant women. Studies in animals have shown toxic effects on offspring when exposed during pregnancy. Fertile women must use adequate contraception during treatment with zonisamide, and for one month after discontinuation.
Use during breast-feeding	The effect of zonisamide in breast-fed babies is unknown.
Use in elderly patients	Elderly patients appear to be more susceptible to adverse effects such as swelling of legs and hands and intense itching than younger patients. They may also be more susceptible to serious skin erruptions and allergic reactions.
Effects on growth and development in children and teenagers *[Developmental and maturational impairment in children and adolescents]*	Weight loss (see above) may lead to delayed growth and maturation/development in children and teenagers. Weight decreases and delayed bone development has been observed with zonisamide.

Missing information

Risk	**What is known**
Use in patients with poor liver function *[Use in patients with hepatic impairment]*	The effect of zonisamide in patients with poor liver function has not been studied.
Use in children below 6 years of age	The safety and benefits of zonisamide have not been established in patients below 6 years or weighing less than 20 kg.

VI.2.5 Summary of additional 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 Summary of Product Characteristics and the Package leaflet for Zonisamide hard capsules can be found in Zonisamide 25 mg, 50 mg and 100 mg hard capsules' EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan (if applicable)

None are planned.

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

Version	Date	Safety Concerns	Comment
V1	22-Jun-16	Use during breast-feeding to be included as an important potential risk	-As per RMS Day 70 recommendation