VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Epilepsy is a brain disorder that causes people to have recurring seizures. Epilepsy has many possible causes, including illness, brain injury, and abnormal brain development and in many cases, the cause is unknown. The seizures happen when the normal pattern of neuronal activity becomes disturbed,

causing strange sensations, emotions, and behavior or sometimes convulsions, muscle spasms, and loss of consciousness. Seizures can be classified as simple, where the patient remains aware, or complex, where awareness is lost, and may be associated with secondary tonic clonic generalization. The prevalence of epilepsy is 5 to 10 per 1,000 population; 60% of those affected have partial seizures. Up to 40% of patients with epilepsy continue to have seizures in spite of receiving antiepileptic drug (AED) treatment and those with partial seizures are among the most difficult to treat.

VI.2.2 Summary of treatment benefits

Adults

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults

The clinical efficacy of adjunctive zonisamide therapy has been established in four pivotal, phase III, randomized, double-blind, placebo-controlled trials, of periods of up to 24 weeks with either once or twice daily dosing, which together included approximately 850 patients, aged 12-77 years, with refractory partial epilepsy. In all four trials, zonisamide 300-600 mg/day resulted in significant reductions in median total seizure rates vs placebo. The median reduction in partial seizure frequency is related to zonisamide dose with sustained efficacy at doses of 300-500 mg per day (Brodie et al, 2012).

Monotherapy in partial seizures, with or without secondary generalisation

Efficacy of zonisamide as monotherapy for adults with newly diagnosed partial epilepsy was established based on the results of a randomized, double-blind, non-inferiority trial, comparing zonisamide to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures. In this trial, once-daily monotherapy with zonisamide (200-500 mg/day) has been shown to be non-inferior to, and as well tolerated as, twice-daily monotherapy with controlled-release carbamazepine (400-1200 mg/day) in adults with newly diagnosed partial epilepsy. Zonisamide has also been shown to have favourable long-term retention rates, an important indication of its overall effectiveness (Brodie et al, 2012).

Paediatric Population

Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adolescent and paediatric patients (aged 6 years and above)

In paediatric patients (aged 6 years and above), efficacy has been demonstrated with zonisamide in a double-blind, placebo-controlled study, which included 207 subjects and had a treatment duration of up to 24 weeks. A 50% or greater reduction from baseline in seizure frequency during the 12-week stable dose period was seen in 50% of the zonisamide-treated subjects and 31% of the patients on placebo.

Zonisamide in clinical practice

Additionally, several studies have demonstrated that adjunctive treatment with zonisamide is effective when administered under everyday clinical practice conditions, with a favourable safety/tolerability profile similar to that observed in clinical trials. In the Zonisamid im Alltag Der Epilepsiepatienten (ZADE) study, almost 80% of patients showed a reduction in seizure frequency of $\geqslant$50% over a median follow-up of 18 weeks, and over one-third of patients became seizure free. Data from these clinical practice studies also indicate that zonisamide is effective and generally well tolerated when administered as a first-line adjunctive treatment and is associated with high retention rates and improvements in quality of life. Evidence from these clinical practice studies therefore complements data from zonisamide's clinical trial programme, providing pragmatic information on the likely benefits and risks of treatment under real-life conditions (Duppont and Stefan, 2012).

VI.2.3 Unknowns relating to treatment benefits

Zonisamide must be added to existing therapy for paediatric patients aged 6 years and above. Effectiveness of monotherapy with zonisamide in the treatment of seizures in paediatric population has not been established.

The safety and efficacy of zonisamide in children aged below 6 years or those below 20 kg have not yet been established.

There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

Specific safety issues encountered in the paediatric studies, and specifically weight loss, may have deleterious implications for growth and development, and may lead to general deterioration of health. Altogether, data on effects on long-term growth and development are limited.

Caution should be exercised at initiation of treatment in elderly patients and patients with renal impairmnet as there is limited information on the use of zonisamide in these patients.

There are no adequate data from the use of zonisamide in pregnant or breast-feeding women and the potential risk for these patients is unknown. Zonisamide must not be used during pregnancy or breast-feeding unless clearly necessary, in the opinion of the physician, and only if the potential benefit is considered to justify the risk.

Also, neither the safety and efficacy nor the pharmacokinetics of zonisamide has been studied in patients with impaired liver function. Therefore use in patients with severe hepatic impairment is not recommended and caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of zonisamide may be required.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity reactions	In some predisposed patients the active ingredient or the excipients of a drug can elicit a state of altered reactivity in which the body reacts with an exaggerated immune response to what is perceived as a foreign substance. This is known as hypersensitivity reaction. The clinical characteristics of drug hypersensitivity reactions are very heterogeneous, and can vary from mild to quite severe and even fatal reactions. Any drug is assumed to be able to elicit hypersensitivity reactions, but antibiotics and antiepileptics are the drugs most frequently causing them. With zonisamide, cases of hypersensitivity, drug-induced hypersensitivity syndrome, and drug rash with eosinophilia and systemic symptoms have been reported.	By using the product with caution following the SPC and Packaging Leaflet indications. Zonisamide Uriach is contraindicated for any patient with known hypersensitivity to the active substance, to any of the excipients of the product, or to sulphonamides. Any patient taking zonisamide who develops signs and symptoms of a hypersensitivity reations must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic drugs. Dose reduction (including therapy discontinuation if necessary) should be considered.
Skin eruptions	Many drugs can cause immune skin reactions. Specifically, the anticonvulsant or antiepileptic drugs are known to cause	By using the product with caution following the SPC and Packaging Leaflet indications. Consideration must be given to

Risk	What is known	Preventability
	frequent skin adverse events. In the case of zonisamide, approximately 1 in 20 people who take it have a red rash within the first few weeks of treatment. The rash may take various forms, from small red spots or blotches on the surface of the skin to large blisters. It may be preceded or accompanied by itchiness. Although it is quite rare for the rash to be serious, no rash should be ignored since it can evolve to more serious and life-threatening conditions causing skin failure and death, as Stevens-Johnson syndrome or toxic epidermal necrolysis.	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 concomitant antiepileptic agents that may independently induce skin rashes.
Hematologic events	Zonisamide contains a sulphonamide group in its chemical structure. Medicinal products containing a sulphonamide group have the potentially to induce serious immune based haematological disturbances, including aplastic anaemia, which very rarely can be fatal. Cases of ecchymosis, agranulocytosis, aplastic anaemia, leucocytosis, leucopoenia, lymphadenopathy, pancytopenia, and thrombocytopenia have been reported with zonisamide..	By using the product with caution following the SPC and Packaging Leaflet indications. Zonisamide Uriach is contraindicated for any patient with known hypersensitivity to the active substance, to any of the excipients, or to other sulphonamides. Any patient taking zonisamide who develops signs and symptoms of hypersensitivity reactions must be closely supervised and dose reduction (including therapy discontinuation if necessary) should be considered.
Kidney stones	Some patients taking zonisamide, especially those with a predisposition to have kidney stone, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Kidney stone formation after zonisamide have occurred also in paediatric patients Kidney stones may lead to chronic renal damage. Risk factors include prior stone formation, a family history of	By using the product with caution following the SPC and Packaging Leaflet indications. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Renal ultrasound should be performed at the discretion of the physician. In the event kidney stones are detected, zonoisamide should be discontinued

Risk	What is known	Preventability
	nephrolithiasis and high levels of calcium. In addition, patients taking other medications associated with kidney stone formation may be at increased risk.	
Disordered body temperature (oligohidrosis and hyperthermia) and dehydration	Zonisamide can cause children to sweat less and overheat and if children are not treated this can lead to brain damage and death. Children are most at risk especially in hot weather. Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. 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 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. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures and strenuous physical exercise depending on the condition of the patient. Prescribers should draw the attention of paediatric patients and their parent/carers to the advice in the Packaging Leaflet on preventing heatstroke and overheating in children as provided.	By using the product with caution following the SPC and Packaging Leaflet indications. Particularly, when children are taking zonisamide, some precautionary measures should be follow: they should stay cool and must avoid heavy exercise especially when the weather is hot, must drink plenty of cold water, and must not take medicinal products that predispose patients to heat related disorders, as carbonic anhydrase inhibitors (like topiramate and acetazolamide) and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin). If child's skin feels very hot with little or no sweating, child becomes confused, has muscle cramps, or heartbeat or breathing become rapid, some urgent measures must be taken: • Take the child to a cool, shaded place • Sponge the child's skin with cool (not cold) water • Give the child cold water to drink • Seek urgent medical assistance In the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature, discontinuation of zonisamide should be considered.
Pancreatitis and elevated	In the post-market setting,	By using the product with

Risk	What is known	Preventability
amylase and lipase	clinical signs and symptoms of pancreatitis have been reporter very rarely (in less that 1 in 10000 patients) in people taking zonisamide.	caution following the SPC and Packaging Leaflet indications. In patients taking zonisamide who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of zonisamide be considered and appropriate treatment initiated.
Muscle disorders	Since it is in the market, some cases of rhabdomyolysis and blood creatine phosphokinase increased (both conditions indicating a possible muscle damage) have been reporterd very rarely (in less that 1 in 10000 patients) in people taking zonisamide.	By using the product with caution following the SPC and Packaging Leaflet indications. When severe muscle pain and/or weakness develop, either in the presence or absence of a fever, in patients taking zonisamide, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that zonisamide discontinuation be considered and appropriate treatment initiated.
Weight loss	Zonisamide may cause weight loss. The incidence of decreased body weight is consistent across age groups affecting both adult and paediatric patients. However, the potential seriousness of weight loss in more important in children, where this weight loss may lead to deterioration of general condition and affects bone maduration. In a pooled analysis of safety data on 420 paediatric subjects (183 subjects aged 6 to 11 years, and 237 subjects aged 12 to 16 years with a mean duration of exposure of	By using the product with caution following the SPC and Packaging Leaflet indications. Zonisamide is not recommended for paediatric patients who are underweight (definition in accordance with the WHO age adjusted BMI categories) or have a decreased appetite. Given the potential seriousness of weight loss in children, weight should be monitored in this population. A dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts, otherwise

Risk	What is known	Preventability
	approximately 12 months) the incidence of a decrease in body weight of 10% or more was 10.7%. There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long term effect of weight loss in the paediatric population on growth and development is unknown.	zonisamide should be discontinued.
Metabolic acidosis and its potential for osteopenia	Metabolic acidosis is associated with zonisamide treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of zonisamide in placebo-controlled clinical trials and in the post-marketing period. Generally, zonisamide-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. The amounts by which bicarbonate is decreased are usually small – moderate, and rarely patients can experience more severe decreases. Conditions or therapies that predispose to acidosis may be additive to the bicarbonate lowering effects of zonisamide. The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in paediatric and adolescent patients. Moreover, the long term effect of low bicarbonate levels on growth and development is unknown. In a controlled study and its	By using the product with caution following the SPC and Packaging Leaflet indications. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in patients who are at an increased risk of adverse consequences of metabolic acidosis, in patients with symptoms suggestive of metabolic acidosis, or in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or medicinal products). Zonisamide should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction. In paediatric and adolescent patients, appropriate evaluation and monitoring of serum bicarbonate levels should be carried out. Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and

Risk	What is known	Preventability
	open label extensiona, a 70.4% of paediatric subjects (6 to 17 years) who received zonisamide had at least one treatment-emergent bicarbonate measurement below 22mmol/L. The duration of low bicarbonate measurements was also long (median 188 days)	acetazolamide. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing zonisamide (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop. If the decision is made to continue patients on zonisamide in the face of persistent acidosis, alkali treatment should be considered.
Suicide/suicidal thoughts	Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for zonisamide. Cases of suicidal ideation and suicide attempt have been uncommonly repoted with zonisamide.	By using the product with caution following the SPC and Packaging Leaflet indications. 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	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 concomitant antiepileptic medicines once seizure control with zonisamide has been achieved in the add-on situation, in order to reach monotherapy with zonisamide. Therefore, withdrawal of concomitant anti-epileptic medicinal products must be undertaken with caution. Also, when zonisamide treatment is to be discontinued, it should be withdrawn gradually. In clinical studies of adult patients, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses (where necessary). In clinical studies of paediatric patients, down-titration was completed by dose reductions at weekly intervals in increments of about 2 mg/kg.
Effects on ability to drive and use machines	No studies on the effects on the ability to drive and use machines have been performed. However, given that some patients may

Risk	What is known (Including reason why it is considered a potential risk)
	experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase, caution is advised during activities requiring a high degree of alertness, e.g., driving or operating machines.
Use in renal impairment	In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance <20 ml/min. Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of zonisamide might be required. Since zonisamide and its metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.
Pregnancy issues	There are no adequate data from the use of zonisamide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Zonisamide must not be used during pregnancy unless clearly necessary, in the opinion of the physician, and only if the potential benefit is considered to justify the risk to the foetus. The need for anti-epileptic treatment should be reviewed in patients planning to become pregnant. If zonisamide is prescribed, careful monitoring is recommended. Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential should be given specialist advice regarding possible effects of zonisamide on the foetus and the risk should be discussed with the patient in relation to the benefits before starting treatment. The risk of birth defect is increased by factor 2 to 3 in the offspring of mothers treated with an antiepileptic medicinal product The most frequently reported are cleft lip, cardiovascular malformations and neural tube defect. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy. No sudden discontinuation of anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child.
Use in the elderly	Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of zonisamide in these patients. Prescribers should also take account of the safety profile of zonisamide. Clinically data showed no significant differences in the plasma levels between young and elderly patients. However, a pooled analysis of safety data on 95 elderly subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus compared to the adult population. Review of post-marketing data suggests that patients aged 65 years or older report a higher frequency than the general population of the following events: Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome.
Developmental and maturational impairment in children and adolescents	Some specific safety issues, as decreased appetite and weight loss were encountered in the paediatric studies. In placebo-controlled clinical studies the incidence of a decrease in body weight of 10% or more was 10.7%. These effects and specifically weight loss may have deleterious implications for growth and development, and may lead to general deterioration of health. Altogether, data on effects on long-term growth and development are limited.

Missing information

Risk	What is known
Limited information on use in impaired liver function.	Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower increment of doses of zonisamide may be required.
Limited information on use in children below 6 years.	The safety and efficacy of zonisamide in children aged below 6 years or those below 20 kg have not yet been established. There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics (SmPC) of Zonisamide Uriach, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them, as well as an abbreviated version of this in the form of a package leaflet (PL), can be found in the Health Agencies web pages and are also included in Annex II of this RMP.

Zonisamide has not any special requirement conditions and restrictions for its safe and effective use and thus additional risk minimisation measures are not deemed necessary.

VI.2.6 Planned post authorisation development plan

Currently, no further post-authorisation efficacy studies are planned.

No study have been imposed as a condition of the marketing authorisation

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable. This is the first version of Zonisamide Uriach RMP.