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 behaviour 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 people; 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. Together the trials 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 the 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 ≥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.

Caution should be exercised at initiation of treatment in elderly patients and patients with renal impairment, 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.

Use of zonisamide in patients with impaired liver (hepatic) function has not been studied. 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	Predisposed patients may react with an exaggerated immune response to the active ingredient, or to the excipients, of a drug. This is known as a hypersensitivity reaction. The clinical characteristics may vary from mild to quite severe and even fatal reactions. 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 Package Leaflet indications. Zonisamid EQL Pharma 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 reaction 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	Anticonvulsant drugs are known to cause frequent skin adverse events. In the case of zonisamide, approximately 1 in 20 people using zonisamide gets 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.	By using the product with caution following the SPC and Package Leaflet indications. 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 concomitant antiepileptic agents that may independently induce skin rashes. 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, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Risk	What is known	Preventability
Hematologic events	Sulphonamides, such as zonisamide, have the potential to induce serious immune based haematological disturbances, including aplastic anaemia, which very rarely may be fatal. Cases of ecchymosis, agranulocytosis, aplastic anaemia, leucocytosis, leucopoenia, lymphadenopathy, pancytopenia, and thrombocytopenia have been reported in connection with zonisamide use.	By using the product with caution following the SPC and Package Leaflet indications. The possible occurrence of blood disorders should be monitored by blood tests. Patients taking zonisamide who feel unusually tired or feverish, have a sore throat, swollen glands, or find that their bruise more easily, should contact their doctor as soon as possible as this may mean they have a blood disorder.
Kidney stones	Patients using zonisamide, including paediatric patients, may be at increased risk of renal stone formation. Kidney stones may lead to renal colic and even chronic renal damage. Risk factors include prior stone formation, a family history of nephrolithiasis, high levels of calcium, or concomitant medications associated with kidney stone formation.	By using the product with caution following the SPC and Package 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, zonisamide should be discontinued.
Disordered body temperature (oligohidrosis and hyperthermia) and dehydration	Zonisamide may decrease the body's ability to sweat and decreases the body’s ability to cool down. This is more common in paediatric patients, and especially in warm weather. Overheating may result in heat stroke. Some cases of heat stroke induced by zonisamide requiring hospital treatment have been reported.	By using the product with caution following the SPC and Package Leaflet indications. While taking zonisamide, some precautionary measures should be followed: Children should stay cool and must avoid heavy exercise, must drink plenty of cold water, and must not take medicinal products that predispose them to heat related disorders, such as carbonic anhydrase inhibitors (like topiramate and acetazolamide) and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).

Risk	What is known	Preventability
		If the child's skin feels very hot with little or no sweating, the 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, oligohidrosis, or elevated body temperature, discontinuation of zonisamide should be considered.
Pancreatitis and elevated amylase and lipase	In the post-market setting, clinical signs and symptoms of pancreatitis have been reported very rarely (in less that 1 in 10 000 zonisamide patients.	By using the product with caution following the SPC and Package Leaflet indications. In patients using zonisamide who develop the clinical signs and symptoms of pancreatitis such as severe pain in the stomach or back, it is recommended to monitor pancreatic lipase and amylase levels. If pancreatitis is evident, and in the absence of another obvious cause, it is recommended to discontinue zonisamide and to initiate an appropriate treatment.
Muscle disorders	Some cases of rhabdomyolysis and increased blood creatine phosphokinase (both conditions indicating a possible muscle damage) have been reported very rarely (in less than 1 in 10 000 zonisamide patients.	By using the product with caution following the SPC and Package Leaflet indications. When severe muscle pain and/or weakness develops in patients taking zonisamide, either in the presence or absence of a fever, it is recommended to assess markers of muscle damage,

Risk	What is known	Preventability
		including serum creatine phosphokinase and aldolase levels. If these enzymes are elevated, and in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended to discontinue zonisamide and to initiate an appropriate treatment.
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 it may lead to deterioration of general condition and affects bone maturation. In a pooled analysis of safety data on 420 paediatric subjects 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.	By using the product with caution following the SPC and Package 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 zonisamide should be discontinued.
Metabolic acidosis and its potential for osteopenia	Metabolic acidosis has been observed with the use of zonisamide in placebo-controlled clinical trials and in the post-marketing period. Generally, the amounts by which bicarbonate is decreased are small to moderate, and rarely patients may experience a more severe decrease of bicarbonate. The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in paediatric and adolescent patients. In a controlled study, 70.4% of paediatric subjects (6 to 17 years) who received	By using the product with caution following the SPC and Package Leaflet indications. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in paediatric and adolescent patients, and in adult patients who are at an increased risk (such as patients with renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or therapies that predispose to acidosis). In paediatric and adolescent patients, zonisamide should not

Risk	What is known	Preventability
	zonisamide had at least one treatment-emergent bicarbonate measurement below 22mmol/L. The duration of low bicarbonate measurements was also long (median 188 days).	be used as co-medication with other carbonic anhydrase inhibitors such as topiramate and acetazolamide. In adult patients, zonisamide should be used with caution together with carbonic anhydrase inhibitors, as there is insufficient data to rule out a pharmacodynamic interaction. 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 despite 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 does not exclude the possibility of an increased risk for zonisamide. Cases of suicidal ideation and suicide attempt have been uncommonly reported for patients using zonisamide.	By using the product with caution following the SPC and Package Leaflet indications. Patients should be monitored for signs of suicidal ideation and behaviour 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. Only insufficient data exist concerning 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. 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 performed 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 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	Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients. A slower titration of zonisamide might be required. Since zonisamide and its metabolites are excreted renally, zonisamide 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. 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 this patient group. A pooled analysis of safety data on 95 elderly

Risk	What is known (Including reason why it is considered a potential risk)
	subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus in the elderly 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, such as decreased appetite and weight loss have been seen 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. Therefore zonisamide is not indicated in children below 6 years. 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 Zonisamid EQL Pharma, 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 does not have 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 has 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 the Zonisamid EQL Pharma RMP.