EUROPEAN UNION RISK MANAGEMENT PLAN FOR ZONEGRAN (ZONISAMIDE)

Risk Management Plan Version to be Assessed as Part of This Application:

Risk Management Plan (RMP) version number:	12.1
Data lock point for this RMP:	31 Mar 2020
Date of final sign-off:	04 Jan 2021
Rationale for submitting an updated RMP:	Updated data lock point for this updated RMP per RMP template guidance by European Medicines Agency (EMA) and Rev 2.0.1 accompanying Good Pharmacovigilance Practices (GVP) Module V Rev 2. Updated post-authorisation data exposure to reflect updated data lock point. Moved summary of safety concerns in Part VI within subsection II.A "List of Important Risks and Missing Information" per the RMP template guidance by EMA and Rev 2.0.1 accompanying GVP Module V Rev 2.

SUMMARY OF SIGNIFICANT CHANGES IN THIS RMP:

Part/Module/Annex	Major Change(s)	Version Number and Date
Risk Management Plan Version to be Assessed as Part of This Application	Updated the data lock point for this RMP in accordance with the RMP template guidance by EMA and Rev 2.0.1 accompanying GVP Module V Rev 2.	12.1, 04 Jan 2021
Part II: Safety Specification		
Part II: Module SV: Postauthorisation Experience	Updated post-authorisation data exposure to reflect updated data lock point.	12.1, 04 Jan 2021
Part VI: Summary of the Risk Management Plan	Moved summary of safety concerns in Part VI within subsection II.A "List of Important Risks and Missing Information" per the RMP template guidance by EMA and Rev 2.0.1 accompanying GVP Module V Rev 2.	12.1, 04 Jan 2021

Other RMP versions under evaluation:	Not applicable
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Version number:	11.2
Approved with procedure:	
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Qualified Person for Pharmacovigilance (QPPV) Name:	
QPPV oversight declaration	The content of this RMP has been reviewed and approved by QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GVP	Good Pharmacovigilance Practices
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (international non-proprietary name [INN] or common name)	Zonisamide
Pharmacotherapeutic group(s) (Anatomic Therapeutic Classification [ATC] Code)	Antiepileptic N03AX15
Marketing Authorisation Holder	[redacted]
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zonegran®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is a benzisoxazole derivative structurally unrelated to currently marketed AEDs.
	Summary of mode of action: Zonisamide is an antagonist of voltage-dependent sodium and calcium channels, which is thought to decrease neuronal excitability, thereby acting to prevent the onset, or reduce the spread of seizures.
	Important information about its composition: The active substance is zonisamide. Excipient with known effect: each hard capsule contains 0.75 mg hydrogenated vegetable oil (from soyabean).
Hyperlink to the Product Information	https://www.ema.europa.eu/documents/product-information/zonegran-epar-product-information_en.pdf
Indication(s) in the EEA	Current (if applicable): Zonegran is indicated as: Monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy. Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.
	Proposed (if applicable): Not applicable

Table 1 Product Overview

Dosage in the EEA	Current (if applicable): Posology - Adults Dosage escalation and maintenance Zonegran may be taken as monotherapy or added to existing therapy in adults. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 1 of the SmPC. Some patients, especially those not taking cytochrome P450 3A4 (CYP3A4)-inducing agents, may respond to lower doses. Withdrawal When Zonegran treatment is to be discontinued, it should be withdrawn gradually (see Section 4.4 of the SmPC). 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). See Table 1 (Adults – recommended dosage escalation and maintenance regimen) of the SmPC. General dosing recommendations for Zonegran in special patient populations Paediatric population (aged 6 years and above) Dosage escalation and maintenance Zonegran must be added to existing therapy for paediatric patients aged 6 years and above. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 2 of the SmPC. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses. Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke (see Section 4.4 of the SmPC: Paediatric Population). Note: See Table 2 (Paediatric population [aged 6 years and above] – recommended dosage escalation and maintenance regimen) of the SmPC. To ensure a therapeutic dose is maintained the weight of a child should be monitored and the dose reviewed as weight changes occur up to a weight of 55 kg. The dose regime is 6-8 mg/kg/day up to a maximum dose of 500 mg/day. The safety and efficacy of Zonegran 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. Withdrawal When Zonegran treatment is to be discontinued, it should be withdrawn gradually (see Section 4.4 of the SmPC). In clinical studies of paediatric patients, down-titration was completed by dose reductions at weekly intervals in increments of about 2 mg/kg (ie, in accordance with the schedule in Table 3 of the SmPC). Elderly Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of Zonegran in

Table 1 Product Overview

	these patients. Prescribers should also take account of the safety profile of Zonegran (see Section 4.8 of the SmPC). Patients with renal impairment 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 Zonegran 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. 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. Patients with hepatic impairment 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 titration of Zonegran may be required.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Hard capsules containing 25, 50, or 100 mg zonisamide. ODT containing 25, 50, 100, or 300 mg zonisamide (approved in the EU but not launched).
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

AED = antiepileptic drug, ATC = Anatomic Therapeutic Classification, CYP3A4 = cytochrome P450 3A4, EEA = European Economic Area, INN = international non-proprietary name, ODT = orodispersible tablet, SmPC =Summary of Product Characteristics.

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2 Summary of Epidemiology of Partial Seizures, With or Without Secondary Generalisation

Incidence of target indication	Developed countries: 40 to 70 per 100,000 person years. Usually higher in younger children (0-10 years) and in older people (over 65 years) (Sander, 2003; MacDonald, et al., 2000; Forsgren, et al., 2005; Duncan, et al., 2006). Resource-poor countries: >120 per 100,000 person years (de Boer, et al., 2008). -In North America, age-adjusted incidence: 16-51 per 100,000 person years (Benn, et al., 2008; Hauser, et al., 1993). -In South America, rural Chile, age-adjusted incidence: 111 per 100,000 person years (Lavados, et al., 1992). -European studies age-adjusted incidence: 26 (Norway [de Graaf, 1974]) to 47 (England [Klenerman, et al., 1993]) per 100,000 person years. -In Asia, India, age-adjusted incidence: 35 per 100,000 person years (Mani, et al., 1998). -In Africa, age-adjusted incidence: 43 (Ethiopia [Tekle-Haimanot, et al., 1997]) to 51 (Tanzania [Rwiza, et al., 1992]) per 100,000 person years. No significant differences in age-adjusted incidence of epilepsy over time have been noticed (Hauser, et al., 1980; Banerjee, et al., 2009). Many studies report a higher incidence in males than females but seldom has this difference been significant (Krohn, 1963). However, other articles have reported that cumulative incidence for all unprovoked seizures reported in Iceland and US demonstrates a significant male excess (Krohn, 1963; Olafsson, et al., 2005). No statistically significant differences in incidence among non-Hispanic Whites, African Americans, Hispanics, and Asians were noted in a study based on Health Maintenance Organization enrolees and their families in the US, eliminating much of the influence of socioeconomic status (Annegers, et al., 1999). Similarly, a study estimating incidence of epilepsy in an urban community found similar rates in Hispanics, Whites and African Americans (Shackleton, et al., 1999). Partial or localisation-related epilepsies account for 20% - 66% of incident epilepsies in population-based studies of all ages (Krohn, 1963; Zieliński, 1974; Olafsson, et al., 1998; Granieri, et al., 1983; Joensen, 1986). Incidence of partial seizures for people younger than 60 years is 20 cases per 100,000 person years and for persons aged 60-80 years it increases to 80 cases per 100,000 person years (Carroll and Benbadis, 2009).

Table 2 Summary of Epidemiology of Partial Seizures, With or Without Secondary Generalisation

Prevalence of target indication	Worldwide, at least 50 million people are estimated to have epilepsy (World Health Organization, 2001; Leonardi and Ustun, 2002). More than 80% of those live in developing countries, where the condition remains largely untreated (Meinardi, et al., 2001). Partial seizures are more prevalent in countries where cysticercosis is prevalent (Swinkels, et al., 2001). Age-adjusted prevalence in studies that used door-to-door survey methodology ranged from 2.2 in India (Koul, et al., 1988) to 41.0 per 1000 in Nigeria (Longe and Osuntokun, 1989). In the North American studies, the age-adjusted prevalence was 5.0 in New York (Kelvin, et al., 2007) and 7.1 per 1000 in Mississippi (Haerer, at al., 1986). In Central and South America, the overall age-adjusted prevalence ranged from 3.7 per 1000 in Argentina (Melcon, et al., 2006) to 22.2 per 1000 in Ecuador (Cruz, et al., 1985). In Europe, age-adjusted prevalence was low, 2.7 to 3.3 per 1000 in Italy (Reggio, et al., 1996; Meneghini, et al., 1991) when compared to a prevalence of 7.0 per 1000 in the Kucukcekmece Region of Istanbul, Turkey (Onal, et al., 2002). In a study conducted in Copiah County, Mississippi, age-adjusted prevalence was higher for African-Americans (8.2 per 1000) as compared to Caucasians (5.4 per 1000), not accounting for the socioeconomic status (Hirsch, et al., 2006). A UK study found the prevalence of epilepsy to be lower in South Asians (3.6 per 1000) in comparison to non-South Asians (7.8 per 1000; OR=0.46; 95% CI: 0.38-0.57) (Wright, et al., 2000). In studies conducted in North America (Hirsch, et al., 2006; Hauser, et al., 1991) and Europe (White, et al., 1979; Birbeck and Kalichi, 2004; Jalava and Sillanpää, 1996; Dunn, et al., 1999; Olafsson and Hauser, 1999; Giuliani, et al., 1992; Luengo, et al., 2001; Rocca, et al., 2001; Gallitto, et al., 2005; Li, et al., 2008), partial seizures constitute 12% to 62% (~35% most commonly reported estimate) of all epilepsies. In Central and South America, they range from 20% to 92% (Zieliński, 1974; Chan, et al., 1990; Nicoletti, et al., 1999; Medina, et al., 2005) in Asia 8% to 54%; (Hyson and Sadler, 1997; Bharucha, et al., 1988; Karaagaç, et al., 1999) in Africa 3% to 71% of all epilepsies (Olafsson, et al., 1998; Osuntokun, et al., 1987; Tekle-Haimanot, et al., 1990; Attia-Romdhane, et al., 1993; Dent, et al., 2005).
Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease	Most reports show a general trend towards an increase in prevalence during adolescence or early adulthood (Zieliński, 1974; Yanez-Rubal, et al., 2002; Birbeck and Kalichi, 2004). In developed countries, most studies show the prevalence of epilepsy to be stable in the adult age groups and to increase with age after 50 (White, et al., 1979; Guberman, et al., 1999). In most studies in developing countries, prevalence of epilepsy remains stable in the third to fourth decades and typically drops after the fifth decade of life. In a few studies, prevalence then again increases after age 40 (Zieliński, 1974; Yanez-Rubal, et al., 2002; Canger, et al., 1999). A majority of studies report higher prevalence in males than females. However, absolute difference in gender-specific prevalence is minimal.
The main existing treatment options	Many patients' partial seizures are treated with combinations of AEDs. However, despite the variety of currently marketed AEDs, epilepsy is not totally controlled for over a third of patients. Current treatments also have clinically relevant tolerability issues. Up to a quarter of the patients initially exposed to an AED will have adverse effects severe enough to require drug withdrawal. It is therefore important to keep all treatment options for treatment of partial seizures available to treating physicians in order to effectively treat partial onset seizures with medicines that offer a wide mechanism of action either in monotherapy or combination therapy.

Table 2 Summary of Epidemiology of Partial Seizures, With or Without Secondary Generalisation

Natural history of the indicated condition in the population, including mortality and morbidity	Chronic epilepsy patients have an increased risk of premature death (Sander, 2004; Lhatoo, et al., 2001). Symptomatic epilepsy may reduce life expectancy by up to 18 years (Gaitatzis, et al., 2004). The mortality rate among individuals with epilepsy is 2-3 times that of the general population. Most deaths are due to the underlying cause of epilepsy with remainder due to accidents, SUDEP, and suicides. SUDEP occurs with no apparent cause. The annual incidence of SUDEP is 1 in 2500 persons with mild epilepsy and 1 in 250 persons with severe epilepsy (Swinkels, et al., 2001). In a large cohort study of all patients over 15 years old, in whom a diagnosis of epilepsy was recorded at discharge from any hospital in Stockholm during 1980-1989, a SMR of 3.6 (CI: 3.5-3.7) was estimated (Nilsson, et al., 1997) In a retrospective study of the survival status of outpatients seen in a Dutch epilepsy center over a 40-year period (38,665 person years, 404 deaths), the SMR was 3.2 (CI: 2.9-3.5) (Shackleton, et al., 2002). SMRs for institutionalized populations (ie, patients living in residential epilepsy centers) range between 1.9 and 3.0 (Gerstner, et al., 2007; Klenerman, et al., 1993; White, et al., 1979). The proportion of deaths due to epilepsy is higher in selected population studies (proportional mortality ratio: 18%-41% [Henriksen, et al., 1967; Iivanainen and Lehtinen, 1979; Shackleton, et al., 1999; Krohn, 1963]) than in community studies (1%-13%) (Asconapé, et al., 1993; Zieliński, 1974; Hauser, et al., 1980; Harvey, et al., 1993; Sillanpää, et al., 1998). Mortality was not increased in Rochester patients with complex partial seizures with or without generalisation (SMR=1.5, not statistically significant) (Mendez and Doss, 1992). In Iceland, idiopathic cases with partial seizures (all types combined) did not have an increased mortality (SMR=1.5; 95% CI 0.7-2.8) (Olafsson, et al., 1998). In Sweden, partial seizures were associated with an increased mortality (SMR=2.1; 95% CI: 1.2-3.6) when all etiologies were considered together (Lindhout and Omtzigt, 1994). In most studies, mortality was higher in males with epilepsy than in females (U.S. Food and Drug administration, FDA Alert, 2008; Mendez and Doss, 1992; Lindhout and Omtzigt, 1994; Lindsten, et al., 2000). At all ages, the SMR is increased for people with epilepsy compared to referent populations. Most studies have found an inverse relationship between SMR and age (U.S. Food and Drug administration, FDA Alert, 2008; Mendez and Doss, 1992; Hauser and Hesdorffer, 1990). The highest SMRs are found in children, while decreasing SMRs are found with increasing age. However, the highest excess mortality is found in the elderly (47 per 1000 or 8 times higher in 75 years and older than in children) (Nilsson, et al., 2002; Tellez-Zentteno, et al., 2007).
Important comorbidities	• Learning disabilities • Depression • Psychosis • Attention deficit hyperactivity disorder (ADHD) • Generalized anxiety disorders • Social phobia • Panic disorder

AED = antiepileptic drug, OR = Odds Ratio, SMR = Standardized Mortality Ratio, SUDEP = Sudden Unexpected Death in Epilepsy.

Part II: Module SII - Nonclinical Part of the Safety Specification

The key nonclinical safety findings for zonisamide are shown in Table 3.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

	Important Nonclinical Safety Findings	Relevance to Human Usage
Safety Pharmacology		
Body weight gain suppression	Suppression in body weight gain following repeat oral doses of 800 mg/kg/day in mice, 200, 300, and 600 mg/kg/day in rats (accompanied by emaciation/weight loss), and ≥60 mg/kg/day in juvenile rats have been observed.	In clinical studies weight loss has been observed; use of zonisamide in subjects of weight less than 20 kg has not been evaluated.
Toxicity		
Hepatic effects	Findings not observed in clinical studies, but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark brown discoloration, mild hypertrophy, concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation). In rats, increased liver weight and elevations in liver enzymes were observed.	There is no evidence from clinical studies of an adverse effect of zonisamide on hepatic function. However, evaluation of serious adverse event reports identified cholecystitis and cholelithiasis as being possibly causally associated with zonisamide. Additionally, a few spontaneous adverse event reports have been received that suggest that zonisamide may be associated with abnormal liver function test results, although this is difficult to assess in patients who are receiving other AEDs which are recognized to have these effects.
Hematological effects	In a 1-year, oral-toxicity study in rats dosed daily with oral zonisamide doses of 2, 20, and 200 mg/kg/day, significant changes in some of the hematological parameters were observed (decreases in erythrocyte counts and hematocrit and hemoglobin values, with increased neutrophils and decreased leukocytes in the differential counts).	In postmarketing experience, cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia and leukocytosis have been spontaneously reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.
Renal effects	Increased kidney weights were commonly seen in ZNS-treated animals at doses of 200 mg/kg/day and above. No notable histopathological observations were seen except for renal calculi composed primarily of magnesium phosphate in 3/18 male and 1/20 female rats administered 200 mg/kg for 1 year. Elevations in BUN are consistent with the increased kidney weights seen and may be indicative of renal damage. The observed increase in urine volume, and possibly the relative decrease in potassium are consistent with the ability of ZNS to inhibit renal carbonic anhydrase. This diuretic effect is also consistent with the increased water consumption observed in some of the nonclinical studies.[a]	Data from clinical trials indicate that similar elevations in BUN and creatinine have been reported, but these effects in humans are not considered clinically relevant, given the effect is only slight and reversible following cessation of dosing.[a] Events of kidney calculus (3.9%) have been reported in adjunctive use studies.

Table 3 Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	Zonisamide was teratogenic in animal studies. Zonisamide caused developmental abnormalities in mice, rats and dogs and was embryo-lethal in cynomolgus monkeys when administered during the period of organogenesis at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans.	There are no adequate clinical data for the use of ZNS in pregnant women. There have been postmarketing reports of teratogenicity with congenital anomalies and perinatal abnormalities as well as abortions (spontaneous, induced, and elective) with the use of ZNS. The teratogenic effects of ZNS, however, are not clearly defined since the majority of malformations were noted in patients receiving multiple AEDs.
Developmental toxicity	A toxicology study in juvenile animals was undertaken as part of a paediatric development program conducted in fulfillment of a post-approval commitment to the EMA. Zonisamide (doses: 20, 60, and 200 mg/kg/day) was administered to juvenile rats by oral gavage for 10 weeks (administration commencing on Day 7 post partum), and followed by a 4-week recovery period. Adverse effects on body weight and food intake were observed at ≥60 mg/kg; a transient effect on crown to rump length and a delay of male physical (sexual) development at 200 mg/kg was observed and was likely related to decreased body weight. Effects on some behavioral endpoints at 200 mg/kg were generally known effects of zonisamide or were considered related to exaggerated pharmacologic effects of zonisamide, to which there were no neuropathological correlates. Some changes in clinical pathology parameters and histopathological changes in the liver, adrenals and/or kidneys were noted at ≥60 mg/kg, but no unexpected findings were observed. Adverse effects were observed at 200 mg/kg on mating and estrous cycles. The effects, where assessed, typically showed reversibility over a 4-week period, except for histopathological changes in kidneys at 200 mg/kg, which only showed partial reversibility, and some behavioral changes at 200 mg/kg when assessed after 1 to 2 weeks of recovery. Based on the results, the NOAEL for ZNS in this study was 20 mg/kg. At this dose, at the end of the treatment period, the C_{max} was 15.5 and 17.5 µg/mL in males and females, respectively, and the area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{(0-24h)}$) was 205 µg•h/mL in both sexes.	Results from Phase 3 studies and pooled paediatric data (Study E2090-044-312 and Study E2090-044-313) indicate the use of ZNS to be generally safe and well tolerated when used as adjunctive therapy in children and adolescents 6 to <18 years of age. The majority of SAEs and other significant events were transient and manageable. No notable effects of ZNS on growth were reported. However, long-term human data on bone and sexual maturation are missing and therefore no solid conclusions regarding these parameters can be made.

AED = antiepileptic drug, $AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24 hours, BUN = blood urea nitrogen, EMA = European Medicines Agency, MAA = Marketing Authorisation Application, NOAEL = No Observed Adverse Effect Level, SAE = serious adverse event, ZNS = zonisamide.

a. EU MAA, Section 2.4.4.3.2.

Part II: Module SIII - Clinical Trial Exposure

Table 4 Number of Subjects Exposed to Zonisamide in Clinical Studies

Indication	Population type / Submission Status Category (see footnotes)[a]	Completed / Terminated
Epilepsy	1. Adjunctive use in adults (Primary safety database Oct 2003)	1132
	2. Monotherapy in adults (Study 310 & 304)	359
	3. Use in the elderly (Elderly pooled analysis May 2011)	95
	4. Use in children & adolescents (Paediatric pooled analysis Dec 2011)	398
	5. Adjunctive use in paediatrics (Study E2090-E044-313)	72
	Total Individual Epilepsy Subjects[a]	2056
Healthy volunteers	6. Submitted with MAA (not included in pooled analysis)	356
	7. Submitted during post-approval procedures	150
	8. Not submitted to EMA	32
Migraine	6. Submitted during post-approval procedures	174
Neuropathic pain	6. Submitted during post-approval procedures	35
Parkinson's Disease	6. Submitted during post-approval procedures	351
	Overall Total	3154

EMA = European Medicines Agency, MAA = Marketing Authorisation Application.

1. Primary safety database (Oct 2003) comprises individual zonisamide-exposed adult subjects from studies 810-922, 912-EUR, 912-US, AN46046-302, 720-02385-96 (912-39), 720-02385-96 EXT (912-39 EXT), 810-920, 810-921, 810-921 EXT, 810-922 EXT, 912-99, 912-EUR EXT, 912-US EXT.
2. Monotherapy in adults includes 359 individual adult zonisamide-exposed subjects from studies E2090-E044-310 (257 adult subjects) and AN46046-304 (102 adult subjects). Subjects enrolled in the extension phases of these studies (ELN46046-355 and Study E2090-E044-314) were not included in this count.
3. The elderly pooled analysis (May 2011) includes individual zonisamide-exposed elderly subjects from studies 810-921, 810-922, AN46046-302, E2090-E044-401, E2090-E044-402, AN46046-304, and E2090-E044-310.
4. The pediatric pooled analysis (Dec 2011) includes individual zonisamide-exposed paediatric subjects from studies: 810-920, 810-921, 810-921-Ext, 810-922, AN46046-225, AN46046-226, AN46046-302, AN46046-304, AN46046-353, AN46046-354, AN46046-355, E2090-044-312, ZNS-401, ZNS-501, ZNS-502, ZNS-504, and ZNS-505.
5. Adjunctive use in paediatrics (Aug 2012) includes 72 subjects newly exposed to zonisamide from Study E2090-E044-313.
6. Submitted with MAA (not included in pooled analysis) comprises studies that were submitted either with the initial MAA or in response to questions but were not considered suitable for inclusion in the pooled analysis.
7. Submitted during post-approval procedures comprises studies that were submitted either as full reports in fulfilment of follow-up measures or in synoptic form in fulfilment of follow-up measure DNR 20.
8. Not submitted to EMA includes studies that were either ongoing at, or had started after, the time of follow-up measure DNR 20, or for which the study report is not available in English.

a. This table does not include adult subjects from epilepsy studies that were not included in the original pooled analysis (either because they were not suitable for pooling or because they were completed after submission of the initial MAA), and therefore, is an underestimate.

Table 5 Zonisamide Exposure in Studies Involving Epilepsy Subjects

Study	Number of Subjects		
	Zonisamide	Placebo	Individual zonisamide
Controlled Studies			
Total in Controlled Studies	498	350	498
Uncontrolled (Open-Label) Studies in Primary Safety Database (including compassionate use)			
Total in Open-label Studies	1269	0	709
Total Unique Zonisamide Exposed Subjects			1207[a]

MAA = Marketing Authorisation Application.

a: The pooled analysis included subjects from the following studies: 810-922, 912-EUR, 912-US, AN46046-302, 720-02385-96 (912-39), 720-02385-96 EXT (912-39 EXT), 810-920, 810-921, 810-921 EXT, 810-922 EXT, 912-99, 912-EUR EXT, 912-US EXT.

Source: EU MAA, Table 2.7.4.3 and Section 2.7.4.1.1.3.

Table 6 Exposure in Subject Years of Exposure

Duration of Zonisamide Therapy	Zonisamide Dose (mg/day)							
	≤100 N=1154	>100-200 N=1089	>200-300 N=945	>300-400 N=1010	>400-500 N=773	>500-600 N=487	>600 N=236	All Doses N=1207
Subject years of exposure[a]	74.8	57.6	139.5	343.9	292.2	316.6	282.7	1507.3

MAA = Marketing Authorisation Application, N = Number of subjects in dose grouping.

a. The subject years of exposure have been calculated from the sum of the durations of treatment within each of the dose ranges for all subjects who received treatment with zonisamide at a dose within each range. Subjects can, therefore, be included in more than one dose group.

Source: EU MAA, Table 2.7.4.5.

Table 7 Exposure Duration by Dose

Duration of Zonisamide Therapy	Zonisamide Modal Dose (mg/day)[b]							
	≤100 N=94	>100-200 N=50	>200-300 N=137	>300-400 N=324	>400-500 N=283	>500-600 N=201	>600 N=118	All Doses N=1207
>0-1 month (1-30 days)	21 (22.3)	14 (28.0)	5 (3.6)	4 (1.2)	6 (2.1)	0 (0.0)	0 (0.0)	50 (4.1)
>1-2 months (31-60 days)	4 (4.3)	8 (16.0)	15 (10.9)	8 (2.5)	9 (3.2)	4 (2.0)	1 (0.8)	49 (4.1)
>2-3 months (61-90 days)	3 (3.2)	11 (22.0)	18 (13.1)	49 (15.1)	27 (9.5)	9 (4.5)	1 (0.8)	118 (9.8)
>3-6 months (91-182 days)	5 (5.3)	10 (20.0)	23 (16.8)	90 (27.8)	50 (17.7)	20 (10.0)	9 (7.6)	207 (17.1)
>6-12 months (183-365 days)	57 (60.6)	3 (6.0)	51 (37.2)	65 (20.1)	121 (42.8)	46 (22.9)	23 (19.5)	366 (30.3)
>1-2 years (366-730 days)	4 (4.3)	3 (6.0)	12 (8.8)	60 (18.5)	36 (12.7)	60 (29.9)	32 (27.1)	207 (17.1)
>2-3 years (731-1095 days)	0 (0.0)	1 (2.0)	1 (0.7)	19 (5.9)	14 (4.9)	21 (10.4)	8 (6.8)	64 (5.3)
>3-5 years (1096-1825 days)	0 (0.0)	0 (0.0)	1 (0.7)	11 (3.4)	9 (3.2)	16 (8.0)	20 (16.9)	57 (4.7)
>5-7 years (1826-2555 days)	0 (0.0)	0 (0.0)	10 (7.3)	14 (4.3)	10 (3.5)	23 (11.4)	18 (15.3)	75 (6.2)
>7 years (>2555 days)	0 (0.0)	0 (0.0)	1 (0.7)	4 (1.2)	1 (0.4)	2 (1.0)	6 (5.1)	14 (1.2)

MAA = Marketing Authorisation Application, N = Number of subjects in dose grouping.

a. Duration is measured from start of zonisamide therapy. Subjects who continued from one study to another (eg., those subjects who entered into an extension study) are counted once by total duration of zonisamide therapy.

b. Subjects are grouped according to most frequently used (modal) dose of zonisamide.

Source: EU MAA, Table 2.7.4.4.

Table 8 Adjunctive Use in Adults: Demographic Characteristics in Epilepsy Studies

Characteristic		N=1207
Sex [n (%)]	Male	650 (53.9)
	Female	557 (46.1)
Age category [n (%)]	12-17 years	61 (5.1)
	18-65 years	1132 (93.8)
	>65 years [a]	13 (1.1)
Age at screening (years)	Mean (Standard Deviation)	34.5 (11.6)
	Median	33.4
	Range	12 to 79

MAA = Marketing Authorisation Application, N = Number of subjects in dose grouping.

a. These elderly subjects are also included in the exposure section for the pooled analysis of elderly data.

Source: EU MAA, Table 2.7.4.7.

Table 9 Demographic Characteristics of Patients in Zonisamide Clinical Trials

Race	N=1207 (%)
White	1091 (90.4)
Black	58 (4.8)
Hispanic	30 (2.5)
Asian	9 (0.7)
Other	19 (1.6)

MAA = Marketing Authorisation Application, N = Number of subjects in dose grouping.

Source: EU MAA, Section 2.7.4.7.

Table 10 Adjunctive Use in Adults: Clinical Trial Exposure by Special Populations

Population	Persons [n]; N = 1207	Person time (person-days)[a]
Pregnant women	14	-
Lactating women	0	-
Renal impairment (total)	23	-
Cr-CL greater than 60 mL/min	8	-
Cr CL 20–60 mL/min	8	-
Cr-CL below 20 mL/min	7	-
Hepatic impairment	2	-
Cardiac impairment	0	-
Sub-populations with genetic polymorphism	0	-

Cr-CL = Creatinine clearance, N = Number of subjects in dose grouping.

a. Person time could not be estimated due to limited data for duration of exposure.

Table 11 Monotherapy Use in Adults: Clinical Trial Exposure by Duration

Duration of exposure	Persons [n (%)]; N = 281	Person time[a] (person-days)
All subjects exposed for at least 1 day	281 (100%)	88,366
All subjects exposed for at least 61 days	248 (88.3%)	87,574
All subjects exposed for at least 151 days	219 (77.9%)	84,516
All subjects exposed for at least 331 days	178 (63.3%)	74,704
All subjects exposed for at least 691 days	3 (1.1%)	2233

N = Number of subjects in dose grouping.

a. Person time is the sum of exposure from study entry to study completion/discontinuation for all subjects who remained in the study at each time point.

Source: Clinical Study Report E2090-E044-310. Table 14.4.1, Listing 16.2.9.7, and Appendix 16.2.5.

Table 12 Monotherapy Use in Adults: Clinical Trial Exposure by Final Dose

Dose of exposure (final dose attained)	Persons [n (%)]; N = 281	Person time (person-days)
100 mg	15 (5.3)	162
200 mg	17 (6.0)	1678
300 mg	197 (70.1)	66,749
400 mg	27 (9.6)	10,739
500 mg	25 (8.9)	9038

N = Number of subjects in dose grouping.

Source: Clinical Study Report E2090-E044-310, Table 14.4.3.

Table 13 Monotherapy Use in Adults: Clinical Trial Exposure by Age Group and Sex

Age group	**Persons [n (%)]; N = 281**		**Person time (person-days)**	
	M	**F**	**M**	**F**
Adults 18-64 years	160 (56.9)	97 (34.5)	53,393	28,437
Elderly aged ≥65 years[a]	14 (5.0)	10 (3.6)	3077	3459

F = female, M = male, N = Number of subjects in dose grouping.

a. These elderly subjects are also included in the exposure section for the pooled analysis of elderly data.

Source: Study E2090-0044-310.

Table 14 Monotherapy Use in Adults: Clinical Trial Exposure by Special Populations

Population	**Persons [n]; N = 281**	**Person time[a] (person-days)**
Pregnant women	1	-
Lactating women	0	-
Renal impairment	0	-
Hepatic impairment	0	-
Cardiac impairment	0	-
Sub-populations with genetic polymorphism	0	-

N = Number of subjects in dose grouping.

a. Person time was not estimated due to the limited number of subjects.

Source: Study E2090-0044-310.

Table 15 Overall Use in the Elderly: Clinical Study Exposure by Duration

Duration of exposure	**Persons [n (%)]; N = 95**	**Person time[a] (person-days)**
All subjects exposed for at least 1 day	95 (100%)	16,009
All subjects exposed for at least 61 days	86 (90.5%)	15,890
All subjects exposed for at least 151 days	74 (77.9%)	15,084
All subjects exposed for at least 331 days	32 (33.7%)	9588
All subjects exposed for at least 691 days	15 (15.8%)	6449

N = Number of subjects in dose grouping.

a. Person time is the sum of exposure from study entry to study completion/discontinuation for all subjects who remained in the study up to each time point. Duration in 402 was 5 months.

Source: Clinical Study Report E2090-E044-402 Table 14.4.1 and Listing 16.2.9.11, other studies: elderly pooled analysis.

Table 16 Overall Use in the Elderly: Clinical Study Exposure by Final Dose

Dose of exposure (maximum dose achieved in Maintenance Period for 402, last dose for other studies)	Persons [n (%)]; N = 95	Person time (person-days)
Did not reach Maintenance Period [a]	5 (5.3)	113
0 mg [b]	3 (3.2)	440
100 mg	24 (25.3)	2,941
150 mg	2 (2.1)	219
200 mg	19 (20.0)	1,826
250 mg	3 (3.2)	338
300 mg	27 (28.4)	7103
400 mg	6 (6.3)	1546
500 mg	5 (5.3)	924
600 mg	1 (0.1)	559

N = Number of subjects in dose grouping.

[a] Those subjects that did not reach Maintenance Period in E2090-E044-402 reached maximum doses of 50 mg (3 subjects) and 100 mg (2 subjects) in the Titration Period.

[b] All subjects with 0 mg were last dose, suspected to be after a down titration.

Source: Clinical Study Report E2090-E044-402, Table 14.4.4.

Table 17 Overall Use in the Elderly: Clinical Trial Exposure by Age Group and Sex

Age group	Indication	Persons [n (%)]; N = 95		Person time (person-days)	
		M	F	M	F
Elderly aged ≥65 years	Adjunctive therapy	28 (42.4)	31 (57.6)	3,466	3,720
	Monotherapy	23 (63.9)	13 (36.1)	4,992	3,831
	Total	39 (41.0)	56 (59.0)	6,948	9,061

F = female, M = male, N = Number of subjects in dose grouping.

Source: Study Report E2090-E044-402 Table 14.4.1 and Listing 16.2.9.11, other studies: elderly Integrated Safety Summary analysis.

Table 18 Overall Use in the Paediatric Population: Clinical Trial Exposure by Duration

Age group:	<6 years		6 – 11 years		12 – 16 years		Total	
Duration of exposure[a]	Persons [n (%)]; N = 45	Person time (person-months)	Persons [n (%)]; N = 183	Person time (person-months)	Persons [n (%)]; N = 237	Person time (person-months)	Persons [n(%)]; N = 465	Person time (person-months)
At least 1 day	45 (100)	578	183 (100)	2302	237 (100)	2885	465 (100)	5765
≥1 month	43 (95.6)	577	177 (96.7)	2297	214 (90.3)	2870	434 (93.3)	5744
≥3 months	37 (82.2)	565	157 (85.8)	2257	174 (73.4)	2798	368 (79.1)	5620
≥6 months	29 (64.4)	534	127 (69.4)	2127	133 (56.1)	2616	289 (62.2)	5278
≥12 months	20 (44.4)	458	105 (57.4)	1933	105 (44.3)	2377	230 (49.5)	4768
≥24 months	8 (17.8)	249	12 (6.6)	342	23 (9.7)	959	43 (9.2)	1551
≥36 months	2 (4.4)	84	1 (0.5)	37	13 (5.5)	673	16 (3.4)	793
≥48 months	0 (0.0)	0	0 (0.0)	0	6 (2.5)	396	6 (1.3)	396
≥60 months	0 (0.0)	0	0 (0.0)	0	5 (2.1)	345	5 (1.1)	345
≥72 months	0 (0.0)	0	0 (0.0)	0	2 (0.8)	151	2 (0.4)	151

N = Number of subjects in dose grouping.

Table 19 Overall Use in the Paediatric Population: Clinical Trial Exposure by Final Dose

Age group:	<6 years		6 – 11 years		12 – 16 years		Total	
Final Dose of Exposure (mg/kg)	**Persons [n (%)]; N = 45**	**Person time (person-months)**	**Persons [n(%)]; N = 183**	**Person time (person-months)**	**Persons [n(%)]; N = 237**	**Person time (person-months)**	**Persons [n(%)]; N = 465**	**Person time (person-months)**
0 - <5 mg/kg	3 (6.7)	6	19 (10.4)	132	59 (24.9)	339	81 (17.4)	477
5 - <9 mg/kg	12 (26.7)	99	86 (47.0)	1060	103 (43.5)	1396	201 (43.2)	2556
9 - <12 mg/kg	10 (22.2)	153	38 (20.8)	464	53 (22.4)	748	101 (21.7)	1365
12 - <16 mg/kg	16 (35.6)	233	31 (16.9)	446	15 (6.3)	272	62 (13.3)	952
16 - <20 mg/kg	2 (4.4)	35	5 (2.7)	114	4 (1.7)	114	11 (2.4)	263
≥20 mg/kg	2 (4.4)	51	4 (2.2)	85	0 (0.0)	0	6 (1.3)	136

N = Number of subjects in dose grouping.

Source: Paediatric Pooled Analysis, Ad hoc table Exposure by Final Dose.

Table 20 Overall Use in the Paediatric Population: Clinical Trial Exposure by Age Group and Sex

Age group:	<6 years		6 – 11 years		12 – 16 years		Total	
Gender	**Persons [n (%)]; N = 45**	**Person time (person-months)**	**Persons [n (%)]; N = 183**	**Person time (person-months)**	**Persons [n (%)]; N = 237**	**Person time (person-months)**	**Persons [n (%)]; N = 465**	**Person time (person-months)**
Male	30 (66.7)	357	107 (58.5)	1265	123 (51.9)	1480	260 (55.9)	3102
Female	15 (33.3)	221	76 (41.5)	1037	114 (48.1)	1405	205 (44.1)	2663

N = Number of subjects in dose grouping.

Source: Paediatric Pooled Analysis, Ad hoc table Exposure by Age Group and Sex.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 21 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Clinically significant laboratory abnormality (other than those attributed to administration of AEDs)	In the clinical trial setting, subjects with clinically significant abnormalities were excluded to prevent the confounding of safety data.	No	The safety profile has been adequately characterised in the zonisamide nonclinical and clinical programme.
A history of non-epileptic seizures (eg, metabolic or pseudo-seizures)	In the clinical trial setting, subjects with a history of non-epileptic seizures were excluded to prevent the confounding of endpoints as zonisamide should be prescribed only to subjects affected by epileptic seizures.	No	Subjects affected by non-epileptic seizures should not be receiving treatment with zonisamide and the safety profile of zonisamide in epileptic seizures has been adequately characterised in the zonisamide nonclinical and clinical programme.
Taking monoamine oxidase inhibitors, antidepressants, or antipsychotics within 14 days (or 5 half-lives of the drug or active metabolite, whichever is the longer) of Visit 1	In the clinical trial setting, subjects taking monoamine oxidase inhibitors, antidepressants, or antipsychotics within 14 days (or 5 half-lives of the drug or active metabolite, whichever is the longer) of Visit 1 were excluded to prevent the confounding of safety data.	No	The safety profile has been adequately characterised in the zonisamide nonclinical and clinical programme.
Active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease that may confound interpretation of the study results	In the clinical trial setting, subjects with active CNS infection, demyelinating disease, degenerative neurological disease, or any progressive CNS disease were excluded to prevent the confounding of safety data.	No	The safety profile has been adequately characterised in the zonisamide nonclinical and clinical programme.
Clinically significant psychiatric illness, or psychological or behavioural problems	In the clinical trial setting, subjects with clinically significant psychiatric illness, or psychological or behavioural problems were excluded to prevent the confounding of safety data.	No	Suicide/suicidal thoughts is included as an important identified risk (Table 33).

Table 21 Important Exclusion Criteria in Pivotal Studies Across the Development Programme

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Acute intermittent porphyria, hemolytic anemia, or G-6-PD deficiency	In the clinical trial setting, subjects with acute intermittent porphyria, hemolytic anemia, or G-6-PD deficiency were excluded to prevent the confounding of safety data.	No	The safety profile has been adequately characterised in the zonisamide nonclinical and clinical programme.
History of alcoholism, drug abuse, or drug addiction	In the clinical trial setting, subjects with history of alcoholism, drug abuse, or drug addiction were excluded to prevent the confounding of safety data.	No	The safety profile has been adequately characterized in the zonisamide nonclinical and clinical programme.
Known hypersensitivity to sulfonamides, dibenzazepine derivatives, or tricyclic antidepressants	Zonegran is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune-based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction, and major haematological disturbances, including aplastic anaemia, which very rarely can be fatal.	No	Hypersensitivity is included as an important identified risk (Table 24).

AED = antiepileptic drug, CNS = central nervous system, G-6-PD = glucose-6-phosphatase dehydrogenase.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme with zonisamide is unlikely to detect certain types of adverse reactions such as rare adverse reactions or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 22 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme. However, in the pooled analysis performed in 2003, 14 pregnancies had been reported during exposure to zonisamide in adjunctive therapy clinical studies (EU MAA, Section 2.7.4.6.2.6). Similarly, in the pivotal monotherapy study, 1 zonisamide-exposed pregnancy was reported.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Two (of a planned 10) subjects with hepatic impairment were enrolled in study RR-Memo-764-01123 (Protocol 912-33), a pharmacokinetic study of zonisamide in patients with alcoholic cirrhosis following a single 300 mg oral dose.
• Patients with renal impairment	Only 23 patients with renal impairment have been investigated. The effects of varying degrees of renal impairment on the pharmacokinetics of a single oral dose of zonisamide were examined in study RR 764-00620.
• Patients with cardiovascular impairment • Immunocompromised patients	Not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	Two of the pivotal adjunctive use studies (912-US, 912-EUR) imposed a limit of no more than 8 primary or secondary generalized tonic, clonic, or tonic-clonic seizures per month. For the other 2 pivotal studies (AN46046-302 and 810-922) and the pivotal monotherapy study no upper seizure limits were imposed.
Population with relevant different ethnic origin	Details of the number of patients exposed to zonisamide in completed clinical studies by race are provided in Module SIII.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical programme.
Paediatric patients	Paediatric studies did not enroll subjects under 6 years of age. Details of the number of patients exposed to zonisamide in completed clinical studies by age are provided in Module SIII.

MAA = Marketing Authorisation Application.

Part II: Module SV - Postauthorisation Experience

SV.1 Postauthorisation Exposure

SV.1.1 Method Used to Calculate Exposure

There has been extensive postmarketing experience with zonisamide in Japan since 1989, in the US since 2000, and in the EU since 2005.

An estimate of the exposure, for countries listed below, is calculated based on the available data on the number of capsules/tablets dispensed as well as World Health Organization (WHO) defined daily dose (DDD) of 200 mg.

Postmarketing exposure data are not available stratified by sex, age or the proportion of the exposure estimated to be in the paediatric population (age range).

Please note that generic zonisamide is currently available in many countries, and since this estimate includes only the zonisamide sold by [redacted] or its partners, this is an underestimate of worldwide exposure.

SV.1.2 Exposure

Due to the multiple times the ownership of zonisamide has changed over its development and marketing history, exposure data from marketed use before 2005 are not available to [redacted] for any region.

The estimated cumulative postmarketing exposure from 01 April 2005 through 31 March 2020 is in excess of 881.4 million patient-days (approximately 2.4 million patient-years).

Exposure by Age Group and Sex

Currently postauthorisation exposure data by age and sex are not available.

Exposure by Dose

Currently postauthorisation exposure data by dose are not available.

Exposure by Country

Zonisamide has marketing approval via the centralised procedure in the EU for adjunctive treatment of partial seizures with or without secondary generalisation in adults, adolescents, and children aged 6 years and above, and to date, the adult use has been launched in 21 EU countries: Austria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lichtenstein, Malta, Netherlands, Norway, Portugal, Slovak Republic, Spain, Sweden, and UK; whilst the paediatric use has been launched in 16 EU countries: Austria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Iceland, Ireland, Netherlands, Norway, Portugal, Slovak Republic, Spain, Sweden and UK.

Zonisamide also has marketing approval via the centralized procedure in the EU for monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy, and to date has been launched in 15 EU countries: Austria, Czech Republic,

Denmark, Finland, Germany, Greece, Hungary, Iceland, Ireland, Netherlands, Norway, Portugal, Slovak Republic, Sweden and UK.

Postmarketing exposure estimates are shown by region (Table 23). It is not possible to estimate cumulative exposure by each country at this stage of the product's life since such data were not included in previous Periodic Safety Update Reports (PSURs). These data are provided by region only using cumulative exposure information from 01 Apr 2005 through 31 Mar 2020. Exposure per indication (approved and off label) is not provided as there is no reliable means of obtaining such data.

Table 23 Cumulative Postmarketing Exposure by Region from 01 Apr 2005 through 31 Mar 2020

Region / Country	Indication and Population	Patient Days	Patient Years
EU	Adjunctive use in adults, adolescents & children aged 6 years and above. Monotherapy in adults	205,980,543	564,330
US	Adjunctive use in adults	79,193,830	216,969
Japan[a]	Adjunctive use and monotherapy in adults and children	543,011,821	1,487,703
South Korea[a]	Adjunctive use and monotherapy in adults and children	53,703,511	147,133

PSUR = Periodic Safety Update Report.

Source: Zonisamide PSUR No. 1 to PSUR No. 17, total reporting period 01 Apr 2005 through 31 Mar 2020.

a. Exposure data for Japan and South Korea include 100-mg tablet consumption only.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

There have been no specific studies looking at abuse potential. Studies of zonisamide in rats and monkeys have provided no evidence of barbiturate-like physical dependence. The adverse event profile of zonisamide contains no AEs that suggest mood-elating effects or other types of AEs that would be suggestive of a potentially desirable CNS side-effect.

The marketing authorisation holder is unaware of any potential for purposeful, personal misuse/substance abuse.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable. This is not the initial RMP for the product.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable. This is not the initial RMP for the product.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable. This is not the initial RMP for the product.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 24 Important Identified Risk: Hypersensitivity

Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of allergic reaction (1.7%), urticaria (0.6%), ulcerative stomatitis (0.3%), and immune system disorder (0.1%) were reported. Monotherapy study: Not applicable. Paediatric pooled analysis: Events of hypersensitivity (2.3%) and drug hypersensitivity (0.3%) were reported. Adjunctive use in paediatrics: Not applicable. Events of hypersensitivity, including allergic reaction, pruritus, stomatitis and vasculitis, have also been spontaneously reported.
Severity	Adjunctive therapy studies: The majority of the events were mild or moderate. One event of urticaria was severe. Monotherapy study: There were no reports of events within this SOC. Paediatric pooled analysis: The majority of events were mild. Adjunctive use in paediatrics: There were no reports of events within this SOC.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Hypersensitivity reactions can cause long-term organ damage including liver damage.
Impact on quality of life	Generally nonserious, most events of hypersensitivity were mild to moderate in severity. There have been rare reports of SAEs.

Table 24 Important Identified Risk: Hypersensitivity

Risk groups or risk factors	Patients aged 65 years or older report a higher frequency than the general population of drug-induced hypersensitivity syndrome. There are also cases where rash recurs when a patient is switched from one aromatic antiepileptic to another, indicating a high level of cross-reactivity. Other factors could include a history of rash on other antiepileptic drugs, and age <13 years.
Preventability	Patients with hypersensitivity to zonisamide, to any of the excipients or to sulphonamides should not receive this medication.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event, SOC = System Organ Class.

Table 25 Important Identified Risk: Skin Eruptions

Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of maculo-papular rash (1.0%), pruritus (2.5%), pustular rash (0.2%), rash (7.0%), skin necrosis (0.1%), and urticaria (0.6%) were reported. Monotherapy study: Events of pruritus (0.7%), purpura (0.4%), and rash (2.1%), were reported. Paediatric pooled analysis: Events of rash (10.3%), eczema (1.5%), dermatitis, dermatitis contact, rash erythematous, rash pruritic, and urticaria (0.5% for each), dermatitis allergic, dermatitis atopic, drug eruption, and rash maculo-papular (0.3% each) were reported. Adjunctive use in paediatrics: Events of acne (0.7%), alopecia (1.4%), dermatitis allergic (2.1%), eczema (1.4%), pityriasis rosea (0.7%), purpura (0.7%), rash papular (1.4%) were reported. Events of skin eruption including SJS, rash, erythema multiforme, TEN, urticaria, maculo-papular rash, drug-induced hypersensitivity syndrome, and hypersensitivity syndrome have also been spontaneously reported.
Severity	Adjunctive therapy studies: The majority of skin reactions were mild or moderate. Some events of pruritus, rash, and urticaria were severe. Monotherapy study: The reports of rash were mild (0.7%), moderate (1.1%), and severe (0.4%). The 2 reports of pruritus were moderate (0.7%). The report of purpura was mild (0.4%). Paediatric pooled analysis: The majority of skin reactions were mild or moderate; 1 event of rash was severe. Adjunctive use in paediatrics: All skin reactions were mild in severity.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	More severe forms of severe skin eruptions including SJS and TEN are associated with hospitalisation and mortality.
Impact on quality of life	Generally nonserious, most events of skin eruptions were mild to moderate in severity. There have been rare reports of SAEs.
Risk groups or risk factors	Patients aged 65 years or older may have a higher frequency than the general population of Stevens-Johnson Syndrome.
Preventability	Consideration must be given to discontinuing Zonegran in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking Zonegran must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented and skin eruptions are not expected to impact the risk-benefit of zonisamide.
Public health impact	No public health impact identified.

SAE = serious adverse event, SJS = Stevens-Johnson Syndrome, TEN = toxic epidermal necrolysis.

Table 26 Important Identified Risk: Hematological Events

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of anemia (0.7%), ecchymosis (5.0%), leukocytosis (0.1%), leukopenia (0.8%), lymphadenopathy (0.5%), and thrombocytopenia (0.2%) were reported. Monotherapy study: Events of anemia (0.4%), ecchymosis (0.4%), leukopenia (0.4%), neutropenia (0.4%), lymphopenia (0.4%) monocytopenia (0.4%), eosinophilia (1.4%), and thrombocytopenia (0.4 %) were reported. Paediatric pooled analysis: Events of thrombocytopenia (0.5%), platelet count decreased (1.0%), neutropenia (0.5%), neutrophil count decreased (0.3%), anemia (0.8%), white blood cell count decreased (0.3%), and disseminated intravascular coagulation (0.3%) were reported. Adjunctive use in paediatrics: Events of eosinophilia (0.7%); eosinophil count increased (1.4%); monocyte count increased (0.7%) were reported. Events of agranulocytosis, aplastic anemia, leukocytosis, leukopenia, pancytopenia, and thrombocytopenia have also been spontaneously reported.
Severity	Adjunctive therapy studies: One event in this SOC (leukopenia) was classified as severe. All other events were mild or moderate. Monotherapy study: All events in the blood and lymphatic disorders SOC were mild (2.5%) or moderate (0.4%). Paediatric pooled analysis: The majority of events in the blood and lymphatic disorders SOC were mild or moderate; 1 event of anemia (0.3%) and 1 of disseminated intravascular coagulation (0.3%) were severe. Adjunctive use in paediatrics: Eosinophilia and eosinophil count increased were mild or moderate in severity; monocyte count increased was mild.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Severe hematologic events, including agranulocytosis and aplastic anemia, can increase the risk for infections and potentially death if untreated.
Impact on quality of life	Generally nonserious, most events of hematological events were mild to moderate in severity. There have been rare reports of SAEs.
Risk groups or risk factors	There is currently no evidence to suggest a subpopulation or risk factor, that some individuals are more susceptible than others. Main risk factors for aplastic anemia (a rare disease condition in which the bone marrow does not produce adequate number of new blood cells), has been correlated with use of an antiepileptic drug, felbamate, were older age, female sex, and white. In addition, history of a serious allergy or toxicity to other anticonvulsants have also been reported as risk factors for aplastic anemia with felbamate use.
Preventability	Awareness of this possibility for appropriate management.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event, SOC = System Organ Class.

Table 27 Important Identified Risk: Kidney Stones

Potential mechanisms	Evaluation of urinalysis parameters in a Phase 1 study in healthy subjects support the putative mechanism that underlies the potentially increased risk of kidney stone formation due to zonisamide's known inhibitory effect upon carbonic anhydrase.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of kidney calculus (3.9%), kidney pain (0.1%), urine abnormality (0.6%), urinary retention (0.7%), urinary tract disorder (1.0%), and urinary tract infection (4.2%) were reported. Monotherapy study: Not applicable. Paediatric pooled analysis: Events of nephrolithiasis (1.0%), hydronephrosis (0.5%), and nephrocalcinosis (0.3%) were reported. Adjunctive use in paediatrics: Events of cystitis noninfective (0.7%), dysuria (0.7%), nephrolithiasis (0.7%), and renal colic (0.7%) were reported. Events of renal and urinary tract calculi as well as accompanying events such as urine abnormalities, hydronephrosis, hematuria, bladder stenosis, urinary tract infection, and renal tubular acidosis have also been spontaneously reported.
Severity	Adjunctive therapy studies: The majority of events of kidney calculus, urinary retention, urinary tract disorder, urinary tract infection were classified as mild to moderate. The event of kidney pain was severe. Monotherapy study: There were no reports of nephrolithiasis, calculus urinary, hydronephrosis, renal failure, or urine abnormality. Paediatric pooled analysis: The majority of events were mild or moderate; 1 event of nephrolithiasis (0.3%) was severe. Adjunctive use in paediatrics: Cystitis noninfective moderate; dysuria and nephrolithiasis mild; renal colic severe.
Reversibility	Kidney stones are not generally reversible and may require medical, invasive, or surgical treatment.
Long-term outcomes	Kidney stones require medical or surgical treatment. Main complications of urolithiasis are usually acute emergency situations including pyonephrosis, urosepsis, or renal failure. Impact on long-term outcome is low. The main long-term risk is renal insufficiency caused by relapsing urolithiasis with relapsing or persistent genitourinary infections, or caused by postrenal obstructions causing reduction of the renal parenchyma.
Impact on quality of life	Generally nonserious, most events of kidney stones were mild to moderate in severity. There have been rare reports of SAEs.
Risk groups or risk factors	Risk factors for the presence of stones in the kidney include prior stone formation, a family history of kidney stones, and a high level of blood calcium. In addition, patients taking other medications associated with kidney stones may be at increased risk.
Preventability	Avoiding concurrent treatment with carbonic anhydrase inhibitors or other medicinal products that may lead to urolithiasis. Using zonisamide with caution in patients who have risk factors for nephrolithiasis. Advising patients to stay hydrated. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

Table 27 Important Identified Risk: Kidney Stones

Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event.

Table 28 Important Identified Risk: Disordered Body Temperature and Dehydration

Potential mechanisms	It has been speculated that by inhibiting carbonic anhydrase, zonisamide may affect sweating by influencing pH dynamics and the availability of ionized calcium in epithelial cells of eccrine sweat glands (Onal, et al., 2002).
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of heat stroke (0.1%) and dry skin (0.9%) were reported. Monotherapy study: Not applicable. Paediatric pooled analysis: Events of pyrexia (18.1%), dehydration (2.3%), hypohidrosis (2.3%), body temperature increased (0.5%), and anhidrosis (0.3%) were reported. Adjunctive use in paediatrics: Events of pyrexia (1.4%) were reported. Isolated events of decreased sweating, elevated body temperature, heat stroke, and dehydration have also been spontaneously reported. There has been 1 fatal report of anhidrosis and hyperthermia in a paediatric patient.
Severity	Adjunctive therapy studies: The events of heat stroke and dry skin were mild. Monotherapy study: There were no reports of hyperthermia, heat stroke, or oligohidrosis. Paediatric pooled analysis: The majority of events of pyrexia, hypohidrosis, body temperature increased and anhidrosis were mild to moderate; 3 events of pyrexia (0.8%) were severe. The events of dehydration were moderate (1.0%) and severe (1.3%). Adjunctive use in paediatrics: Events of pyrexia were mild.
Reversibility	Events of disordered body temperature and dehydration are generally reversible; however, 1 fatal event has been reported.
Long-term outcomes	Events of disordered body temperature and dehydration are generally time limited and reversible; therefore, for the majority of patients, no long-term adverse outcome is expected. However, 1 fatal event has been reported.
Impact on quality of life	Generally nonserious, most events of disordered body temperature and dehydration are generally mild to moderate in severity. There have been rare reports of SAEs and 1 fatality.
Risk groups or risk factors	The isolated reports of decreased sweating and elevated body temperature were mainly in paediatric patients and during periods of warm weather. Dehydration was also noted, mainly in paediatric patients. Patients with oligohidrosis (decreased sweating) are more likely to develop hyperthermia under conditions of heat and physical activity. Children and young adults are at a greater risk of hyperthermia than the elderly because of a higher metabolic rate, greater physical activity, larger body surface area-to-body mass ratio and therefore greater heat gain from the environment on a hot day, and decreased sweating capacity.

Table 28 Important Identified Risk: Disordered Body Temperature and Dehydration

Preventability	Patients or their carers must be warned to maintain hydration, drink more fluids during warm weather, avoid exposure to excessive temperatures, and take measures not to overheat. Caution should be used when zonisamide is prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity. Carbonic anhydrase inhibitors and anticholinergic agents should not be administered to paediatric patients receiving treatment with zonisamide. As per the SmPC, physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke.
Impact on the risk-benefit balance of the product	Events of decreased sweating, elevated body temperature, heat stroke, and dehydration may occur. Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event, SmPC = Summary of Product Characteristics.

Table 29 Important Identified Risk: Pancreatitis and Elevated Amylase and Lipase

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: One event of pancreatitis was reported in an elderly subject. No events isolated/asymptomatic elevation of amylase or lipase were reported. Monotherapy study: No events of pancreatitis or elevated amylase or lipase were reported. Paediatric pooled analysis: One event of pancreatitis (0.3%) was reported. No events of elevated amylase or lipase were reported. Adjunctive use in paediatrics: No events of pancreatitis or elevated amylase or lipase were reported. Isolated events of elevated amylase and lipase levels and pancreatitis have been spontaneously reported.
Severity	Both events of pancreatitis were severe.
Reversibility	Although pancreatitis events can be very severe they can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Events can be severe and have been associated with fatal outcome.
Impact on quality of life	Adverse events of pancreatitis were severe and can be life threatening.
Risk groups or risk factors	Age less than 20 years, using multiple drugs at the same time, chronic encephalopathy (a condition that affects the brain structure), and hemodialysis are possible risk factors. Pancreatitis following valproate treatment (a drug to treat seizures) occurs more frequently in young patients but may occur at any age.
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

Table 30 Important Identified Risk: Muscle Disorders

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of myalgia (1.3%), muscle hemorrhage (0.1%), myasthenia (0.9%), and creatine phosphokinase increased (0.1%) were reported. Monotherapy study: Events of blood creatine phosphokinase increased (1.1%), myalgia (0.7%) were reported. Paediatric pooled analysis: Events of myalgia (0.8%) and blood creatine phosphokinase increased (0.3%) were reported. Adjunctive use in paediatrics: Not applicable. Several events of rhabdomyolysis and elevated serum creatine phosphokinase have also been spontaneously reported.
Severity	Adjunctive therapy studies: The events of creatine phosphokinase increased and muscle hemorrhage were mild. The events of myasthenia and myalgia were mild or moderate. Monotherapy study: The events of blood creatine phosphokinase increased were mild (1.1%) and myalgia were moderate (0.7%). Paediatric pooled analysis: The events of myalgia and blood creatine phosphokinase increased were mild to moderate. Adjunctive use in paediatrics: No events were reported.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Although generally reversible if treated early, rhabdomyolysis may lead to long-term muscular weakness or renal damage.
Impact on quality of life	Generally nonserious, most events of muscle disorders were mild to moderate in severity.
Risk groups or risk factors	None identified.
Preventability	In patients taking zonisamide, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, 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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

Table 31 Important Identified Risk: Weight Loss

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of weight decreased (10.4%) were reported. During the placebo-controlled studies, a higher percentage of zonisamide-treated patients had weight loss greater than the pre-defined change at some time after starting treatment (18.2%) compared with placebo (5.7%). In the placebo-controlled studies, weight decreases of greater than 10 kg were recorded in 1.3% of zonisamide-treated subjects and 0.6% of placebo-treated subjects. Monotherapy study: Events of weight decreased (6.8%) and underweight (0.4%) were reported. Paediatric pooled analysis: Events of decreased appetite (19.6%), weight decreased (7.0%), abnormal loss of weight (0.5%), and malnutrition (0.3%) were reported. The incidence of a decrease in bodyweight of 5% or more was 35.0%; of 10% or more, the incidence was 10.7%. Adjunctive use in paediatrics: Events of weight decreased (6.9%), decreased appetite (4.9%), and anorexia (0.7%) were reported. Events of weight loss have been spontaneously reported.
Severity	Adjunctive therapy studies: The majority of the events of weight decreased were mild and moderate. One report was severe. Monotherapy study: The events of weight decreased were identified as mild (5.0%) or moderate (0.4%), 1 event was severe (0.4%). The event of underweight was mild (0.4%). Paediatric pooled analysis: The majority of events of weight decreased were mild (3.0%) to moderate (2.5%); 5 events were severe (1.3%). The events of abnormal loss of weight were mild (0.5%). Adjunctive use in paediatrics: Events of weight decreased were mild and moderate in severity; decreased appetite was mostly mild; anorexia was mild. No events were severe.
Reversibility	Events of decreased appetite and weight loss can potentially be reversed upon discontinuation of treatment with zonisamide.
Long-term outcomes	Weight loss in children could be an undesirable effect and could have consequences on growth. Weight loss could also be an undesirable effect in adults.
Impact on quality of life	Generally nonserious. There have been few reports of SAEs of decreased appetite or weight loss, the majority of these with outcomes of improvement or complete recovery.
Risk groups or risk factors	There is currently no evidence to suggest a subpopulation or risk factor, that some individuals are more susceptible than others.
Preventability	A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. Zonisamide is not recommended in paediatric patients who are underweight or have a decreased appetite.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event.

Table 32 Important Identified Risk: Metabolic Acidosis and Its Potential for Osteopenia

Potential mechanisms	Renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	In the adjunctive therapy studies, no events of metabolic acidosis or decreased bicarbonate levels were reported. Events of bone disorders (0.3%) and osteoporosis (0.1%) were reported. In the monotherapy study, there were no AEs reported within this HLT and for these PTs. In the paediatric pooled analysis, events of blood bicarbonate decreased (0.5%) and blood chloride increased (0.3%) were reported. As adjunctive use in paediatrics, there were no AEs reported within this HLT and for these PTs. Events of metabolic acidosis have been spontaneously reported.
Severity	Adjunctive therapy studies: One event of bone disorder was severe. The remaining events of bone disorder and osteoporosis were mild to moderate. Monotherapy study: Decreases of serum bicarbonate from baseline of ≥3.5 mEq/L were observed in 51.1% of subjects. Decreases to below 17 mEq/L and by more than 5 mEq/L were observed in 3.8% of subjects. However, none of these laboratory analyses were considered by investigators as AEs. Decreases in serum bicarbonate from baseline (mean −2.8 mmol/L at the Final Visit) were generally small to moderate. Paediatric pooled analysis: All events of blood bicarbonate decreased and blood chloride increased were mild. Decreases of serum bicarbonate from baseline of ≥3.5 mEq/L were observed in 55% of paediatric subjects. A decrease in bicarbonate (≤16 mmol/L and a drop from baseline of ≥6 mmol/L) occurred in 28 subjects (9.4%) during zonisamide treatment. This recovered to within the normal range or to >16 mmol/L for the majority of subjects at the end of treatment (21/28 subjects [75%]). Two subjects had TEAEs of decreased bicarbonate, which were not serious, not severe and did not lead to discontinuation. There were no corresponding reports of respiratory alkalosis or metabolic acidosis with zonisamide treatment. Adjunctive use in paediatrics: Decreases in bicarbonate levels of at least 3.5 mmol/L were observed in 64 (44.4%) subjects overall; a bicarbonate value of less than or equal to 16 mmol/L and a decrease from baseline of at least 6 mmol/L was observed in 4 (2.8%) subjects overall. No TEAEs of decreased bicarbonate were reported. The decreased bicarbonate levels in zonisamide-treated subjects (mean -1.8 mmol/L at Open-label Visit 4) were generally small to moderate.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	Metabolic acidosis if untreated can lead to loss of bone density, resulting in an increased risk of bone fractures, renal osteodystrophy, and bone disease.
Impact on quality of life	Generally nonserious, most events of metabolic acidosis were mild to moderate in severity. There have been rare reports of SAEs.

Table 32 Important Identified Risk: Metabolic Acidosis and Its Potential for Osteopenia

Risk groups or risk factors	Conditions or therapies that predispose to acidosis (excess acid in the body, such as renal [kidney] disease, severe respiratory [lung] disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or drugs) may contribute to acidosis. The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. The role of chronic metabolic acidosis is an important factor in metabolic bone disorders.
Preventability	Remaining alert to chronic metabolic acidosis and its possible bone effects. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis, in patients who are at an increased risk of adverse consequences of metabolic acidosis and in patients with symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Zonegran (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop. If the decision is made to continue patients on Zonegran in the face of persistent acidosis, alkali treatment should be considered. Zonegran should be used with caution in patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate, as there are insufficient data to rule out a pharmacodynamic interaction.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AE = adverse event, HLT = high-level term, PT = Preferred Term, SAE = serious adverse event, TEAE = treatment emergent adverse event.

Table 33 Important Identified Risk: Suicide/Suicidal Thoughts

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of suicidal behavior (0.6%) were reported. Monotherapy study: One event of suicidal ideation (0.4%) was reported. Paediatric pooled analysis: One event of suicidal ideation (0.3%) was reported. Adjunctive use in paediatrics: Not applicable.
Severity	Adjunctive therapy studies: The majority of events of suicidal behavior were severe; 1 event was moderate. Monotherapy study: The single event of suicidal ideation was reported as moderate. Paediatric pooled analysis: The single event of suicidal ideation was reported as moderate. Adjunctive use in paediatrics: No events were reported.
Reversibility	Thoughts of suicidality can potentially be reversed upon discontinuation of treatment with zonisamide.
Long-term outcomes	Current number of events is too small to extrapolate.
Impact on quality of life	There have been rare reports of serious suicidal and self-injurious behaviour in clinical trials in adult patients with partial seizures.
Risk groups or risk factors	High suicide rate among epileptic patients is more closely associated with psychotic behaviours and psychic auras than with major depression or the psychosocial burden of being epileptic. A study has shown an increase in risk of suicide with mental illness and an increase in relative risk with the use of antipsychotic drugs. The risk of suicide may increase with high seizure frequency, antiepileptic drugs, and multiple therapies at the same time.
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	Although the potential public health impact of suicidality in general is always significant, the small number of suicides in patients treated with AEDs does not allow any conclusions about their effect on public health.

AED = antiepileptic drug.

Table 34 Important Potential Risk: Seizures Following Sudden Withdrawal

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	In the adjunctive therapy studies, the monotherapy study, the paediatric pooled analysis, and as adjunctive use in paediatrics, no events of drug withdrawal convulsions were reported.
Severity	No events of seizures following sudden withdrawal have been reported.
Reversibility	In clinical studies, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses. There is limited experience on abrupt withdrawal.
Long-term outcomes	There is limited experience with abrupt withdrawal.
Impact on quality of life	Although there is limited experience with abrupt withdrawal, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus.
Risk groups or risk factors	As with other antiepileptic drugs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus.
Preventability	Gradual dose reduction on withdrawal of zonisamide. Withdrawal of concomitant AEDs must be undertaken with caution.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AED = antiepileptic drug.

Table 35 Important Potential Risk: Effects on Ability to Drive and Use Machines

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of accidental injury (18.7%) were reported, but there were no events of road traffic accidents or impaired driving. Monotherapy study: One event of road traffic accident was reported (0.4%). Paediatric pooled analysis: Events of injuries were reported, but there were no events of road traffic accidents or impaired driving. Adjunctive use in paediatrics: There were no events associated with road traffic accidents or impaired driving. To date, there have been few spontaneous reports of accidents as a consequence of somnolence.
Severity	Adjunctive therapy studies: The majority of events of accidental injury were mild or moderate. Monotherapy study: The single event of road traffic accident was reported as mild (0.4%). Paediatric pooled analysis: The majority of events of injury were mild to moderate. Adjunctive use in paediatrics: The events within this SMQ were noted as moderate and severe.
Reversibility	Events of somnolence are reversible upon discontinuation of treatment with zonisamide.
Long-term outcomes	Somnolence is self-limiting and reversible as an AE, therefore no adverse long-term outcomes are expected for the safety concern of ability to drive and use machines.
Impact on quality of life	Some patients experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase. Based on current experience, somnolence is considered a very common zonisamide-associated adverse event, whereas disturbance in attention is common. It is possible that these adverse events may lead to impairment in the ability to drive and use machines.
Risk groups or risk factors	None identified.
Preventability	Patients must be advised to exercise caution during activities requiring a high degree of alertness, eg, driving or operating machines.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, SMQ = standardised MedDRA query.

Table 36 Important Potential Risk: Use in Patients With Renal Impairment

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Events of acute kidney failure (0.1%) and blood creatinine increased (0.1%) were reported; however, there was limited information to establish association with previous renal impairment. Monotherapy study: Subjects with a history of renal disorder [serum creatinine level of more than 135 µmol/L (1.5 mg/dL at the Screening Visit)] were excluded. No AEs associated with use in renal impairment were observed. There were no reports of renal failure or blood creatinine increased. Paediatric pooled analysis: Events of blood creatinine increased (0.5%) were reported. Adjunctive use in paediatrics: Subjects who had developed a history of renal calculi or renal insufficiency (creatinine level greater than 135 µmol/L (1.5 mg/dL) were excluded. Events of blood creatinine increased (0.7%) were reported.
Severity	During pharmacokinetic clinical studies, subjects with renal impairment showed renal clearance of single doses of zonisamide that were positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance <20 mL/min. Without dose adjustment, this could result in higher frequency and/or severity of zonisamide-associated adverse events in patients with renal impairment.
Reversibility	Not applicable.
Long-term outcomes	Not applicable.
Impact on quality of life	Use of zonisamide in patients with renal impairment could potentially lead to renal failure or can be fatal.
Risk groups or risk factors	Patients with renal impairment.
Preventability	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.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AE = adverse event.

Table 37 Important Potential Risk: Use in Pregnancy

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Characterisation of the Risk	
Frequency	Adjunctive therapy studies: Fourteen pregnancies had been reported during exposure to zonisamide in clinical studies. A congenital anomaly (hypospadia) was reported in 1 case. Monotherapy study: There was 1 instance (0.4%) of pregnancy in a zonisamide-exposed subject. Paediatric pooled analysis: There were 3 events of unintended pregnancy (0.8%) and 1 of pre-eclampsia (0.3%). Events of congenital mitochondrial cytopathy (0.3%) and hydrocele (0.3%) were reported. Adjunctive use in paediatrics: Not applicable. There have been spontaneous reports (including literature reports) of congenital fetal abnormalities during exposure to zonisamide.
Severity	Adjunctive therapy studies: The majority of events of unintended pregnancy were classified as severe. Monotherapy study: The single event of pregnancy was classified as severe. Paediatric pooled analysis: One event of unintended pregnancy was classified as mild; 2 were classified as severe. The event of pre-eclampsia was mild. The events of congenital mitochondrial cytopathy and hydrocele were mild to moderate. Adjunctive use in paediatrics: There were no AEs reported. In the majority of spontaneously reported cases concomitant use of other AEDs was present.
Reversibility	Of the 14 pregnancies, 1 case resulted in a baby with a congenital anomaly (hypospadia) being delivered following a normal birth (the baby's mother took carbamazepine and zonisamide concomitantly throughout the study), 2 spontaneous abortions occurred, 4 therapeutic abortions were performed, 6 were reported as normal births and 1 pregnancy had not yet reached term at the time of the report. In the monotherapy study, the pregnancy in a zonisamide-exposed subject was terminated medically due to abnormal scan results.
Long-term outcomes	Long-term outcome is dependent on the nature of any congenital anomaly.
Impact on quality of life	There is a risk of congenital anomalies in the offspring. The majority of events have occurred in patients on multiple AEDs.
Risk groups or risk factors	Unknown.
Preventability	Zonegran must not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the fetus. The need for antiepileptic treatment should be reviewed in patients planning to become pregnant. If Zonegran is prescribed, careful monitoring is recommended.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AE = adverse event, AED = antiepileptic drug.

Table 38 Important Potential Risk: Use in the Elderly

Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	Evidence from pooled clinical studies and via Study of Zonegran use in elderly and associated questionnaire.
Characterisation of the Risk	
Frequency	Events that were reported by at least 3 subjects in either the monotherapy or adjunctive elderly pooled analysis and had an incidence of at least double that of the monotherapy or adjunctive adult population are described below. In the adult adjunctive use studies and the monotherapy study, events of dizziness were reported for 297 (21.4%) subjects, events of confusional state were reported for 162 (11.7%) subjects, depression 4 (1.6%) subjects, constipation 67 (4.8%) subjects, diarrhoea 114 (8.2%) subjects, fatigue 135 (9.7%) subjects, oedema peripheral 18 (1.3%) subjects, urinary tract infection 52 (3.7%) subjects, nasopharyngitis 100 (7.2%), and pruritus 29 (2.1%) subjects. In the elderly pooled analysis, for the adjunctive use studies and the monotherapy study, events of dizziness were reported for 14 (14.7%) subjects, confusional state 6 (6.3%) subjects, depression 5 (5.3%) subjects, constipation 7 (7.4%) subjects, diarrhoea 6 (6.3%) subjects, fatigue 11 (11.6%) subjects, oedema peripheral 4 (4.2%) subjects, urinary tract infection 4 (4.2%) subjects, nasopharyngitis 8 (8.4%) subjects, and pruritus 6 (6.3%) subjects.
Severity	Events of dizziness (1), back pain (1), and fatigue (1) were severe; the remaining events were mild or moderate.
Reversibility	Depending on the symptoms, reversibility can vary.
Long-term outcomes	Not available.
Impact on quality of life	Depending on the symptoms, quality of life can vary.
Risk groups or risk factors	Due to age-related changes in body composition and physiology, elderly patients might metabolise drugs differently compared to younger patients, leading to a higher rate and intensity of adverse events.
Preventability	Caution should be exercised at initiation of treatment in elderly patients.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

SAE = serious adverse event.

Table 39 Important Potential Risk: Developmental and Maturational Impairment in Children and Adolescents

Potential mechanisms	Adverse events noted with zonisamide such as decreased appetite and weight loss may have an impact on growth and maturation.
Evidence source(s) and strength of evidence	Paediatric pooled analysis from clinical studies and Clinical Study Report E2090-E044-313.
Characterisation of the Risk	
Frequency	Paediatric pooled analysis: No AEs for these PTs were reported. Adjunctive use in Paediatrics: While there were no reports of AEs for these PTs or consistent evidence of delay in transition to the next Tanner stage and in bone maturation, in some cases of weight decrease delays in these parameters were observed.
Severity	Paediatric pooled analysis: No AEs for these PTs were reported. Adjunctive use in Paediatric: No AEs for these PTs were reported.
Reversibility	Events can potentially be reversed upon discontinuation of treatment.
Long-term outcomes	There are limited data available to assess the impact on an individual patient.
Impact on quality of life	There are limited data available to assess the impact on an individual patient.
Risk groups or risk factors	Paediatric patients who are underweight and have a decreased appetite.
Preventability	Remaining alert to adverse events that may impact growth and development.
Impact on the risk-benefit balance of the product	Routine risk minimisation measures have been implemented.
Public health impact	No public health impact identified.

AE = adverse event, PT = Preferred Term.

SVII.3.2 Presentation of the Missing Information

Table 40 Missing Information: Use in Impaired Liver Function

Missing Information: Use in Impaired Liver Function	
Evidence source	Use in patients with liver impairment has not been studied.
Population in need of further characterisation	Section 4.2 of the SmPC notes that 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 titration of Zonegran may be required.

SmPC = Summary of Product Characteristics.

Table 41 Missing Information: Use in Children Below 6 Years

Missing Information: Use in Children Below 6 Years	
Evidence source	There are limited data from clinical studies in patients below the age of 6 years because it is not known for this age group whether the potential benefits are greater than the risks.
Population in need of further characterisation	Section 4.2 of the SmPC notes that the safety and efficacy of zonisamide in children aged below 6 years or those below 20 kg have not yet been established.. Therefore children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

SmPC = Summary of Product Characteristics.

Part II: Module SVIII - Summary of the Safety Concerns

Safety concerns associated with Zonegran are listed in Table 42.

Table 42 Summary of Safety Concerns

Important identified risks	• Hypersensitivity • Skin eruptions • Hematological events • Kidney stones • Disordered body temperature and dehydration • Pancreatitis and elevated amylase and lipase • Muscle disorders • Weight loss • Metabolic acidosis and its potential for osteopenia • Suicide/suicidal thoughts
Important potential risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in patients with renal impairment • Use in pregnancy • Use in the elderly • Developmental and maturational impairment in children and adolescents
Missing information	• Use in impaired liver function • Use in children below 6 years

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance (PV) activities beyond adverse reactions reporting and signal detection are presented in Table 43.

Table 43 Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Questions for reports of Kidney Stones in children and adolescents	Kidney stones	To further characterise the events of kidney stones in children and adolescents treated with zonisamide in the postmarketing environment.
Questions for reports of Oligohidrosis, Heat Stroke, and Hyperthermia in children and adolescents	Disordered body temperature and dehydration	To further characterise events of oligohidrosis, heat stroke, and hyperthermia in children and adolescents treated with zonisamide in the postmarketing environment.
Questions for reports of Metabolic Acidosis in children and adolescents	Metabolic acidosis and its potential for osteopenia	To further characterise events of metabolic acidosis in children and adolescents treated with zonisamide in the postmarketing environment.
Questions for reports of Delayed Physical and/or Mental Development in children and adolescents	Developmental and maturational impairment in children and adolescents	To further characterise delayed physical or mental development in children and adolescents treated with zonisamide in the postmarketing environment.

III.2 Additional Pharmacovigilance Activities

At present, there are no new categories of additional PV studies or activities being proposed in the PV plan.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no newly planned additional PV activities for zonisamide.

PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

No postauthorisation efficacy studies are planned.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 44 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Hypersensitivity	Routine risk communication: SmPC: Section 4.3, Section 4.4, Section 4.8, Section 6.1 Package Leaflet (PL): Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None
Skin Eruptions	Routine risk communication: SmPC: Section 4.4, Section 4.8 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: All patients who develop a rash while taking zonisamide must be closely monitored as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Hematological Events	Routine risk communication: SmPC: Section 4.4, Section 4.8 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None
Kidney Stones	Routine risk communication: SmPC: Section 4.4, Section 4.5, Section 4.8, Section 5.1 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors, as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None

Table 44 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Disordered Body Temperature and Dehydration	Routine risk communication: SmPC: Section 4.2, Section 4.4, Section 4.8 PL: Section 2 (Patient Alert Box), Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the PL) on preventing heatstroke, as per SmPC Section 4.2. Prevention of overheating and dehydration must be managed as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Pancreatitis and Elevated Amylase and Lipase	Routine risk communication: SmPC: Section 4.4, Section 4.8 PL: Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None
Muscle Disorders	Routine risk communication: SmPC: Section 4.4, Section 4.8 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: In cases of severe muscle pain and/or weakness, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels, and managed as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Weight Loss	Routine risk communication: SmPC: Section 4.4, Section 4.8, Section 5.1, Section 5.3 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication, as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None

Table 44 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Metabolic Acidosis and Its Potential for Osteopenia	Routine risk communication: SmPC: Section 4.4, Section 4.5, Section 4.8 PL: Section 2, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in the pediatric population as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Suicide/Suicidal Thoughts	Routine risk communication: SmPC: Section 4.4, Section 4.8 PL: Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate and treatment should be considered, as per SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Important Potential Risk	
Seizures Following Sudden Withdrawal	Routine risk communication: SmPC: Section 4.2, Section 4.4, Section 4.8 PL: Section 3, Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: When treatment is to be discontinued, it should be withdrawn gradually, as per SmPC Section 4.2 and Section 4.4. Other routine risk minimisation measures beyond the Product Information: None
Effects on Ability To Drive and Use Machines	Routine risk communication: SmPC: Section 4.7 PL: Section 2, Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients must be advised to exercise caution during activities requiring a high degree of alertness, eg, driving or operating machines, as per SmPC Section 4.7. Other routine risk minimisation measures beyond the Product Information: None
Use in Patients with Renal Impairment	Routine risk communication: SmPC: Section 4.2, Section 5.2 PL: Section 2, Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: None

Table 44 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Use in Pregnancy	Routine risk communication: SmPC: Section 4.4, Section 4.6 PL: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: None
Use in the Elderly	Routine risk communication: SmPC: Section 4.2, Section 4.8, Section 5.2 PL: Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: None
Developmental and Maturational Impairment in Children and Adolescents	Routine risk communication: SmPC: Section 4.2, Section 4.4, Section 5.1, Section 5.3 PL: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: None
Missing Information	
Use in Impaired Liver Function	Routine risk communication: SmPC: Section 4.2, Section 5.2 PL: Section 2, Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None
Use in Children Below 6 Years	Routine risk communication: SmPC: Section 4.2 PL: Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: None

PL = Package Leaflet, SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 45 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hypersensitivity	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.1 • PL Sections 2 and 4	Routine PV activities
Skin Eruptions	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on monitoring rash • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Hematological Events	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Kidney Stones	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on reducing risk of stone formation • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • PL Sections 2 and 4	Routine PV activities and questionnaire for kidney stones in children and adolescents (Annex 4)
Disordered Body Temperature and Dehydration	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on drawing the attention of paediatric patients and their parents/carers to the Patient Alert Box in the PL • SmPC Section 4.4, where advice is given on prevention of overheating and dehydration • SmPC Section 4.8 • PL Sections 2 (Patient Alert Box) and 4	Routine PV activities and questionnaire oligohidrosis, heat stroke, and hyperthermia in children and adolescents (Annex 4)

Table 45 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pancreatitis and Elevated Amylase and Lipase	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4	Routine PV activities
Muscle Disorders	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on markers of muscle damage • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Weight Loss	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on dietary supplement or increased food intake • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PL Sections 2 and 4	Routine PV activities
Metabolic Acidosis and Its Potential for Osteopenia	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on appropriate evaluation and monitoring of serum bicarbonate levels • SmPC Section 4.5 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities and questionnaire for metabolic acidosis in children and adolescents (Annex 4)
Suicide/Suicidal Thoughts	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on suicidal ideation or behaviour • SmPC Section 4.8 • PL Section 4	Routine PV activities
Seizures Following Sudden Withdrawal	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on gradual withdrawal of treatment • SmPC Section 4.4, where advice is given on gradual withdrawal of treatment • SmPC Section 4.8 • PL Sections 3 and 4	Routine PV activities
Effects on the Ability to Drive and Use Machines	Routine risk minimisation measures: • SmPC Section 4.7, where advice is given on caution during activities requiring a high degree of alertness • PL Sections 2 and 3	Routine PV activities

Table 45 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in Patients with Renal Impairment	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on treating patients with renal impairment • SmPC Section 5.2 • PL Sections 2 and 3	Routine PV activities
Use in Pregnancy	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.6, where advice is given not to use zonisamide during pregnancy unless clearly necessary • PL Section 2	Routine PV activities
Use in the Elderly	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on caution when treating elderly patients • SmPC Section 4.8 • SmPC Section 5.2 • PL Section 3	Routine PV activities
Developmental and Maturational Impairment in Children and Adolescents	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2	Routine PV activities and questionnaire for delayed physical and/or mental development in children and adolescents (Annex 4)
Use in Impaired Liver Function	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 5.2 • PL Sections 2 and 3	Routine PV activities
Use in Children Below 6 Years	Routine risk minimisation measures: • SmPC Section 4.2 • PL Section 2	Routine PV activities

PL = Package Leaflet, PV = pharmacovigilance, SmPC = Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zonegran®.

This is a summary of the risk management plan (RMP) for Zonegran®. The RMP details important risks of Zonegran®, how these risks can be minimised and how more information will be obtained about Zonegran®'s risks and uncertainties (missing information).

Zonegran®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zonegran® should be used.

This summary of the RMP for Zonegran® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zonegran®'s RMP.

I The Medicine and What it is Used for

Zonegran® is authorised for the indication of monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy and as adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above. It contains zonisamide as the active substance and it is given orally as hard capsules.

Further information about the evaluation of Zonegran®'s benefits can be found in Zonegran®'s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/Zonegran.

II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zonegran®, together with measures to minimise such risks and the proposed studies for learning more about Zonegran®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Zonegran® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Zonegran® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zonegran®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Important identified risks	• Hypersensitivity • Skin eruptions • Hematological events • Kidney stones • Disordered body temperature and dehydration • Pancreatitis and elevated amylase and lipase • Muscle disorders • Weight loss • Metabolic acidosis and its potential for osteopenia • Suicide/suicidal thoughts
Important potential risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in patients with renal impairment • Use in pregnancy • Use in the elderly • Developmental and maturational impairment in children and adolescents
Missing information	• Use in impaired liver function • Use in children below 6 years

II.B Summary of Important Risks

Important Identified Risks	
Hypersensitivity	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled (comparing Zonegran® with placebo) and open-label extension (treatment is known to both participants and the investigators) studies. These events have also been observed in the postmarketing setting (outside of a clinical trial).
Risk groups and risk factors	Patients aged 65 years or older report a higher frequency than the general population of drug-induced hypersensitivity syndrome. There are also cases where rash recurs when a patient is switched from one aromatic antiepileptic to another, indicating a high level of cross-reactivity. Other factors could include a history of rash on other antiepileptic drugs, and age <13 years.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.1 • PL Section 2 • PL Section 4
Skin Eruptions	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Patients aged 65 years or older may have a higher frequency than the general population of Stevens-Johnson Syndrome (a skin disorder that can be triggered by medication).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on monitoring rash • SmPC Section 4.8 • PL Section 2 • PL Section 4
Hematological Events	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	There is currently no evidence to suggest a subpopulation or risk factor, that some individuals are more susceptible than others. Main risk factors for aplastic anemia (a rare disease condition in which the bone marrow does not produce adequate number of new blood cells), has been correlated with use of an antiepileptic drug, felbamate, were older age, female sex, and white. In addition, history of a serious allergy or toxicity to other anticonvulsants have also been reported as risk factors for aplastic anemia with felbamate use.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4

Important Identified Risks (continued)	
Kidney Stones	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Risk factors for the presence of stones in the kidney include prior stone formation, a family history of kidney stones, and a high level of blood calcium. In addition, patients taking other medications associated with kidney stones may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on reducing risk of stone formation • SmPC Section 4.5 • SmPC Section 4.8 • SmPC Section 5.1 • PL Section 2 • PL Section 4
Disordered Body Temperature and Dehydration	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	The isolated reports of decreased sweating and elevated body temperature were mainly in paediatric patients and during periods of warm weather. Dehydration was also noted, mainly in paediatric patients. Patients with oligohidrosis (decreased sweating) are more likely to develop hyperthermia under conditions of heat and physical activity. Children and young adults are at a greater risk of hyperthermia than the elderly because of a higher metabolic rate, greater physical activity, larger body surface area-to-body mass ratio and therefore greater heat gain from the environment on a hot day, and decreased sweating capacity.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on drawing the attention of paediatric patients and their parents/carers to the Patient Alert Box in the PL • SmPC Section 4.4, where advice is given on prevention of overheating and dehydration • SmPC Section 4.8 • PL Section 2 (Patient Alert Box) • PL Section 4

Important Identified Risks (continued)	
Pancreatitis and Elevated Amylase and Lipase	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Age less than 20 years, using multiple drugs at the same time, chronic encephalopathy (a condition that affects the brain structure), and hemodialysis are possible risk factors. Pancreatitis following valproate treatment (a drug to treat seizures) occurs more frequently in young patients but may occur at any age.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4
Muscle Disorders	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies.
Risk groups and risk factors	None identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on markers of muscle damage • SmPC Section 4.8 • PL Section 2 • PL Section 4
Weight Loss	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	There is currently no evidence to suggest a subpopulation or risk factor, that some individuals are more susceptible than others.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on dietary supplement or increased food intake • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 4

Important Identified Risks (continued)	
Metabolic Acidosis and Its Potential for Osteopenia	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Conditions or therapies that predispose to acidosis (excess acid in the body), such as renal [kidney] disease, severe respiratory [lung] disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or drugs) may contribute to acidosis. The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients. The role of chronic metabolic acidosis is an important factor in metabolic bone disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on appropriate evaluation and monitoring of serum bicarbonate levels • SmPC Section 4.5 • SmPC Section 4.8 • PL Section 2 • PL Section 4
Suicide/Suicidal Thoughts (Tendency to commit or think about committing suicide)	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies.
Risk groups and risk factors	High suicide rate among epileptic patients is more closely associated with psychotic behaviours and psychic auras than with major depression or the psychosocial burden of being epileptic. A study has shown an increase in risk of suicide with mental illness and an increase in relative risk with the use of antipsychotic drugs. The risk of suicide may increase with high seizure frequency, antiepileptic drugs, and multiple therapies at the same time.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where advice is given on suicidal ideation or behaviour • SmPC Section 4.8 • PL Section 4

Important Potential Risks	
Seizures Following Sudden Withdrawal	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	As with other antiepileptic drugs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on gradual withdrawal of treatment • SmPC Section 4.4, where advice is given on gradual withdrawal of treatment • SmPC Section 4.8 • PL Section 3 • PL Section 4
Effects on Ability to Drive and Use Machines	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	None identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.7, where advice is given on caution during activities requiring a high degree of alertness • PL Section 2 • PL Section 3
Use in Patients with Renal Impairment (Kidney Impairment)	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Patients with renal impairment.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on treating patients with renal impairment • SmPC Section 5.2 • PL Section 2 • PL Section 3
Use in Pregnancy	
Evidence for linking the risk to the medicine	Evidence from placebo-controlled and open-label extension studies. These events have also been observed in the postmarketing setting.
Risk groups and risk factors	Unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.6, where advice is given not to use zonisamide during pregnancy unless clearly necessary • PL Section 2

Important Potential Risks (continued)	
Use in the Elderly	
Evidence for linking the risk to the medicine	Evidence from pooled clinical studies and via Study of Zonegran use in elderly and associated questionnaire.
Risk groups and risk factors	Due to age-related changes in body composition and physiology, elderly patients might metabolise drugs differently compared to younger patients, leading to a higher rate and intensity of adverse events.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, where advice is given on caution when treating elderly patients • SmPC Section 4.8 • SmPC Section 5.2 • PL Section 3
Developmental and Maturational Impairment in Children and Adolescents	
Evidence for linking the risk to the medicine	Paediatric pooled analysis from clinical studies and Clinical Study Report 2090-E044-313.
Risk groups and risk factors	Paediatric patients who are underweight and have a decreased appetite.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2
Missing information	
Use in Impaired Liver Function	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 5.2 • PL Section 2 • PL Section 3
Use in Children Below 6 Years	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • PL Section 2

PL = Package Leaflet, SmPC = Summary of Product Characteristics.

II.C Postauthorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations for Zonegran®.

II.C.2 Other Studies in Postauthorisation Development Plan

There are no studies required for Zonegran®.

PART VII: ANNEXES

TABLE OF CONTENTS

Annex 1 EudraVigilance Interface

Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Table 46 Annex II: Completed Studies

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
E2090□E044□ 501 Category 3	Drug utilisation study to measure the effectiveness of risk minimisation measures in children and adolescents 6 to <18 years of age. (Retrospective Analyses of UK CPRD database for the years 2014 and 2015)	To measure the effectiveness of risk minimisation measures in the paediatric population	2016

CPRD = Clinical Practice Research Datalink.

Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Table 47 Specific Adverse Drug Reaction Follow-up Forms

Title	Date
Questions for reports of Kidney Stones in children and adolescents	14 Jun 2017
Questions for reports of Oligohidrosis, Heat Stroke, and Hyperthermia in children and adolescents	14 Jun 2017
Questions for reports of Metabolic Acidosis in Children and Adolescents	14 Jun 2017
Questions for reports of Delayed Physical and/or Mental Development in children and adolescents	14 Jun 2017

Questions for reports of Kidney Stones in children and adolescents:

Please complete the attached form and provide any missing information.

In addition please provide the following-

1. Weight, height prior to starting Zonisamide and at time of event (or last recorded)

    a. Was height and weight routinely monitored?

2. Was carbonic anhydrase inhibitors (ie topiramate, acetazolamide, dorzolamide, brinzolamide) or anticholinergic drugs (ie atrophine sulfate, dicycloverine hydrochloride, hyoscine butylbromide, propantheline bromide) given at any time during zonisamide treatment

3. Are there any risk factors such as prior stone formation, family history of kidney stones, hypercalciuria, hypocitraturia, or hyperoxaluria?

4. Was the patient ever diagnosed with a renal anomaly

5. Did the kidney stone occur in summer time or winter time?

Questions for reports of Oligohidrosis, Heat Stroke, and Hyperthermia in children and adolescents:

Please complete the attached form and provide any missing information.

In addition please provide the following-

1. Weight, height prior to starting Zonisamide and at time of event (or last recorded). Was weight and height routinely monitored?

2. Was carbonic anhydrase inhibitors (ie topiramate, acetazolamide, dorzolamide, brinzolamide) or anticholinergic drugs (ie atrophine sulfate, dicycloverine hydrochloride, hyoscine butylbromide, propantheline bromide) given at any time during zonisamide treatment

3. Was the weather outside hot?

4. Was the patient involved in exercise?

5. How long did the episode last?

6. Provide relevant laboratory results including if available

   temperature

   zonisamide serum level

   renal function tests such as creatinine, BUN, and GFR

Questions for reports of Metabolic Acidosis in children and adolescents:

Please complete the attached form and provide any missing information.

In addition please provide the following-

Provide any missing information including-

1. Weight, height prior to starting Zonisamide and at time of event (or last recorded). Was height and weight routinely monitored?

2. Was carbonic anhydrase inhibitors (ie topiramate, acetazolamide, dorzolamide, brinzolamide) or anticholinergic drugs (ie atrophine sulfate, dicycloverine hydrochloride, hyoscine butylbromide, propantheline bromide) given at any time during zonisamide treatment

3. Was there vomiting or diarrhea prior to the event?

4. Provide laboratory results especially serum bicarbonate levels

    a. Was serum bicarbonate levels monitored?

5. Did the patient have any risk factors such as renal disease, severe respiratory disorders, chronic diarrhea, toxic ingestion, ketogenic diet, status epilepticus

Questions for reports of Delayed Physical and/or Mental Development in children and adolescents:

Please complete the attached form and provide any missing information.

In addition please provide the following-

1. Weight, height prior to starting Zonisamide and at time of event (or last recorded). Was height and weight routinely monitored?

2. Provide baseline development status prior to initiation of Zonisamide.

3. Was the patient diagnosed with any disease/syndrome prior to the start of zonisamide therapy that could be associated with a delay in physical or mental development.

4. Please provide specific details on the abnormaity

5. Provide any pertinent laboratory or testing results (ie IQ tests, etc)

6. Provide details of birth including medications mother was on during gestation

Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable. There are no planned or ongoing postauthorisation efficacy studies.

Annex 6 Details of Proposed Additional Risk Minimisation Measures (if Applicable)

Not applicable.

Annex 7 Other Supporting Data (Including Referenced Material)

Annegers JF, Dubinsky S, Coan SP, Newmark ME, Roht L. The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations. Epilepsia. 1999 Apr;40(4):502-6.

Asconapé JJ, Penry JK, Dreifuss FE, Riela A, Mirza W. Valproate-associated pancreatitis. Epilepsia. 1993 Jan-Feb;34(1):177-83.

Attia-Romdhane N, Mrabet A, Ben Hamida M. Prevalence of epilepsy in Kelibia, Tunisia. Epilepsia. 1993 Nov-Dec;34(6):1028-32.

Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy - a review. Epilepsy Res. 2009 Jul;85(1):31-45. Epub 2009 Apr 15. Review.

Benn EK, Hauser WA, Shih T, Leary L, Bagiella E, Dayan P, et al. Estimating the incidence of first unprovoked seizure and newly diagnosed epilepsy in the low-income urban community of Northern Manhattan, New York City. Epilepsia. 2008 Aug;49(8):1431-9. Epub 2008 Mar 11.

Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of epilepsy in the Parsi community of Bombay. Epilepsia. 1988 Mar-Apr;29(2):111-5.

Birbeck GL, Kalichi EM. Epilepsy prevalence in rural Zambia: a door-to-door survey. Trop Med Int Health. 2004 Jan;9(1):92-5.

Canger R, Battino D, Canevini MP, Fumarola C, Guidolin L, Vignoli A, et al. Malformations in offspring of women with epilepsy: a prospective study. Epilepsia. 1999 Sep;40(9):1231-6.

Carroll E, Benbadis SR. Complex partial Seizures. EMedicine. 2009. Available at: http://emedicine.medscape.com/article/1183962-overview.

Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol. 1990;126(1):43–7.

Cruz ME, Schoenberg BS, Ruales J, Barberis P, Proano J, Bossano F, et al. Pilot study to detect neurologic disease in Ecuador among a population with a high prevalence of endemic goiter. Neuroepidemiology. 1985;4(2):108-16.

de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav. 2008 May;12(4):540-6. Epub 2008 Feb 14. Review.

de Graaf AS. Epidemiological aspects of epilepsy in northern Norway. Epilepsia. 1974 Sep;15(3):291-9.

Dent W, Helbok R, Matuja WB, Scheunemann S, Schmutzhard E. Prevalence of active epilepsy in a rural area in South Tanzania: a door-to-door survey. Epilepsia. 2005 Dec;46(12):1963-9.

Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet. 2006 Apr 1;367(9516):1087-100. Review.

Dunn N, Wilton L, Shakir S. Stevens-Johnson syndrome and anti-epileptics. Lancet. 1999 Sep 18;354(9183):1033-4.

FDA ALERT [1/31/2008 Updated: 12/16/2008]: Information for Healthcare Professionals: Suicidal Behavior and Ideation and Anti-epileptic Drugs. Postmarket Drug Safety Information for Patients and Providers. U.S. Food and Drug administration. Available at:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100192.htm. Accessed: 11/16/09.

Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol. 2005 Apr;12(4):245-53. Review.

Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand. 2004 Oct;110(4):207-20.

Gallitto G, Serra S, La Spina P, Postorino P, Laganà A, Tripodi F, et al. Prevalence and characteristics of epilepsy in the Aeolian islands. Epilepsia. 2005 Nov;46(11):1828-35.

Gerstner T, Büsing D, Bell N, Longin E, Kasper JM, Klostermann W, et al. Valproic acid-induced pancreatitis: 16 new cases and a review of the literature. J Gastroenterol. 2007 Jan;42(1):39-48. Epub 2007 Feb 16.

Giuliani G, Terziani S, Senigaglia AR, Luccioni G, Foschi N, Maffei C. Epilepsy in an Italian community as assessed by a survey for prescriptions of anti-epileptic drugs: epidemiology and patterns of care. Acta Neurol Scand. 1992 Jan;85(1):23-31.

Granieri E, Rosati G, Tola R, Pavoni M, Paolino E, Pinna L, et al. A descriptive study of epilepsy in the district of Copparo, Italy, 1964-1978. Epilepsia. 1983 Aug;24(4):502-14.

Guberman AH, Besag FM, Brodie MJ, Dooley JM, Duchowny MS, Pellock JM, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia. 1999 Jul;40(7):985-91.

Haerer AF, Anderson DW, Schoenberg BS. Prevalence and clinical features of epilepsy in a biracial United States population. Epilepsia. 1986 Jan-Feb;27(1):66-75.

Harvey AS, Nolan T, Carlin JB. Community-based study of mortality in children with epilepsy. Epilepsia. 1993 Jul-Aug;34(4):597-603.

Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. Epilepsia. 1980 Aug;21(4):399-412.

Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993 May-Jun;34(3):453-68.

Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. Epilepsia. 1991 Jul-Aug;32(4):429-45.

Hauser WA, Hesdorffer D. Epilepsy: frequency, causes and consequences. New York: Demos Publications, 1990.

Henriksen PB, Juul-Jensen P, Lund M. The mortality of epileptics. Acta Neurol Scand. 1967;43:Suppl 31:164-5.

Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Hager M, et al. Predictors of lamotrigine-associated rash. Epilepsia. 2006;47:318–22.

Hyson C, Sadler M. Cross sensitivity of skin rashes with anti-epileptic drugs. CanJ Neurol Sci. 1997;24:245–9.

Iivanainen M, Lehtinen J. Causes of death in institutionalized epileptics. Epilepsia. 1979 Oct;20(5):485-91.

Jalava M, Sillanpää M. Concurrent illnesses in adults with childhood-onset epilepsy: a population-based 35-year follow-up study. Epilepsia. 1996 Dec;37(12):1155-63.

Joensen P. Prevalence, incidence, and classification of epilepsy in the Faroes. Acta Neurol Scand. 1986 Aug;74(2):150-5.

Karaagaç N, Yeni SN, Senocak M, Bozluolçay M, Savrun FK, Ozdemir H, et al. Prevalence of epilepsy in Silivri, a rural area of Turkey. Epilepsia. 1999 May;40(5):637-42.

Kelvin EA, Hesdorffer DC, Bagiella E, Andrews H, Pedley TA, Shih TT, et al. Prevalence of self-reported epilepsy in a multiracial and multiethnic community in New York City. Epilepsy Res. 2007 Dec;77(2-3):141-50.

Klenerman P, Sander JW, Shorvon SD. Mortality in patients with epilepsy: a study of patients in long term residential care. J Neurol Neurosurg Psychiatry. 1993 Feb;56(2):149-52.

Koul R, Razdan S, Motta A. Prevalence and pattern of epilepsy (Lath/Mirgi/Laran) in rural Kashmir, India. Epilepsia. 1988 Mar-Apr;29(2):116-22.

Krohn W. Causes of death among epileptics. Epilepsia. 1963 Dec;4:315-22.

Lavados J, Germain L, Morales A, Campero M, Lavados P. A descriptive study of epilepsy in the district of El Salvador, Chile, 1984-1988. Acta Neurol Scand. 1992 Apr;85(4):249-56.

Leonardi M, Ustun TB. The global burden of epilepsy. Epilepsia. 2002;43 Suppl 6:21-5.

Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Ann Neurol. 2001 Mar;49(3):336-44.

Lindhout D, Omtzigt JG. Teratogenic effects of anti-epileptic drugs: implications for the management of epilepsy in women of childbearing age. Epilepsia. 1994;35 Suppl 4:S19-28.

Lindsten H, Nyström L, Forsgren L. Mortality risk in an adult cohort with a newly diagnosed unprovoked epileptic seizure: a population-based study. Epilepsia. 2000 Nov;41(11):1469-73.

Longe AC, Osuntokun BO. Prevalence of neurological disorders in Udo, a rural community in southern Nigeria. Trop Geogr Med. 1989 Jan;41(1):36-40.

Luengo A, Parra J, Colás J, Rámos F, Carreras T, Fernández-Pozos MJ, et al. Prevalence of epilepsy in northeast Madrid. J Neurol. 2001 Sep;248(9):762-7.

MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain. 2000 Apr;123 (Pt 4):665-76.

Mani KS, Rangan G, Srinivas HV, Kalyanasundaram S, Narendran S, Reddy AK. The Yelandur study: a community-based approach to epilepsy in rural South India--epidemiological aspects. Seizure. 1998 Aug;7(4):281-8.

Medina MT, Durón RM, Martínez L, Osorio JR, Estrada AL, Zúniga C, et al. Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salamá Study. Epilepsia. 2005 Jan;46(1):124-31.

Meinardi H, Scott RA, Reis R, Sander JW; ILAE Commission on the Developing World. The treatment gap in epilepsy: the current situation and ways forward. Epilepsia. 2001 Jan;42(1):136-49.

Melcon MO, Kochen S, Vergara RH. Prevalence and clinical features of epilepsy in Argentina. A community-based study. Neuroepidemiology. 2007;28(1):8-15. Epub 2006 Dec 8.

Mendez MF, Doss RC. Ictal and psychiatric aspects of suicide in epileptic patients. Int J Psychiatry Med. 1992;22(3):231-7.

Meneghini F, Rocca WA, Grigoletto F, Morgante L, Reggio A, Savettieri G, et al. Door-to-door prevalence survey of neurological diseases in a Sicilian population. Background and methods. The Sicilian Neuro-Epidemiologic Study (SNES) Group. Neuroepidemiology. 1991;10(2):70-85.

Nicoletti A, Reggio A, Bartoloni A, Failla G, Sofia V, Bartalesi F, et al. Prevalence of epilepsy in rural Bolivia: a door-to-door survey. Neurology. 1999 Dec 10;53(9):2064-9.

Nilsson L, Ahlbom A, Farahmand BY, Asberg M, Tomson T. Risk factors for suicide in epilepsy: a case control study. Epilepsia. 2002 Jun;43(6):644-51.

Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. Cause-specific mortality in epilepsy: a cohort study of more than 9,000 patients once hospitalized for epilepsy. Epilepsia. 1997 Oct;38(10):1062-8.

Olafsson E, Hauser WA, Gudmundsson G. Long-term survival of people with unprovoked seizures: a population-based study. Epilepsia. 1998 Jan;39(1):89-92.

Olafsson E, Hauser WA. Prevalence of epilepsy in rural Iceland: a population-based study. Epilepsia. 1999 Nov;40(11):1529-34.

Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol. 2005 Oct;4(10):627-34.

Onal AE, Tumerdem Y, Ozturk MK, Gurses C, Baykan B, Gokyigit A, et al. Epilepsy prevalence in a rural area in Istanbul. Seizure. 2002 Sep;11(6):397-401.

Osuntokun BO, Adeuja AO, Nottidge VA, Bademosi O, Olumide A, Ige O, et al. Prevalence of the epilepsies in Nigerian Africans: a community-based study. Epilepsia. 1987 May-Jun;28(3):272-9.

Reggio A, Failla G, Patti F, Nicoletti A, Grigoletto F, Meneghini F, et al. Prevalence of epilepsy. A door-to-door survey in the Sicilian community of Riposto. Ital J Neurol Sci. 1996 Apr;17(2):147-51.

Rocca WA, Savettieri G, Anderson DW, Meneghini F, Grigoletto F, Sicilian Neuro-Epidemiologic Study (SNES) Group, et al. Door-to-door prevalence survey of epilepsy in three Sicilian municipalities. Neuroepidemiology. 2001 Oct;20(4):237-41.

Rwiza HT, Kilonzo GP, Haule J, Matuja WB, Mteza I, Mbena P, et al. Prevalence and incidence of epilepsy in Ulanga, a rural Tanzanian district: a community-based study. Epilepsia. 1992 Nov-Dec;33(6):1051-6.

Sander JW. Infectious agents and epilepsy. In: Knobler S, O'Connor S, Lemon SM, Najafi M, editors. The infectious etiology of chronic diseases: defining the relationship, enhancing the research and mitigating the effects. Washington, DC: National Academic Press; 2004, p. 93-9.

Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003 Apr;16(2):165-70.

Shackleton DP, Westendorp RG, Kasteleijn-Nolst Trenité DG, de Craen AJ, Vandenbroucke JP. Survival of patients with epilepsy: an estimate of the mortality risk. Epilepsia. 2002 Apr;43(4):445-50.

Shackleton DP, Westendorp RG, Trenité DG, Vandenbroucke JP. Mortality in patients with epilepsy: 40 years of follow up in a Dutch cohort study. J Neurol Neurosurg Psychiatry. 1999 May;66(5):636-40.

Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. N Engl J Med. 1998 Jun 11;338(24):1715-22.

Swinkels WA, Kuyk J, de Graaf EH, van Dyck R, Spinhoven P. Prevalence of Psychopathology in Dutch Epilepsy Inpatients: A Comparative Study. Epilepsy Behav. 2001 Oct;2(5):441-7.

Tekle-Haimanot R, Forsgren L, Abebe M, Gebre-Mariam A, Heijbel J, Holmgren G, et al. Clinical and electroencephalographic characteristics of epilepsy in rural Ethiopia: a community-based study. Epilepsy Res. 1990 Dec;7(3):230-9.

Tekle-Haimanot R, Forsgren L, Ekstedt J. Incidence of epilepsy in rural central Ethiopia. Epilepsia. 1997 May;38(5):541-6.

Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007 Dec;48(12):2336-44. Epub 2007 Jul 28.

White SJ, McLean AE, Howland C. Anticonvulsant drugs and cancer. A cohort study in patients with severe epilepsy. Lancet. 1979 Sep 1;2(8140):458-61.

World Health Organization. International Classification of Functional Disability and Health (ICF). Geneva: World Health Organization; 2001.

Wright J, Pickard N, Whitfield A, Hakin N. A population-based study of the prevalence, clinical characteristics and effect of ethnicity in epilepsy. Seizure. 2000 Jul;9(5):309-13.

Yanez-Rubal JC, Estevez-Rodriguez J, Crespo-Lopez MC, Martin-Herranz I. Carbamazepine-induced aplastic anaemia: a case report. Revista de Neurologia. 2002;35:647–9.

Zieliński JJ. Epilepsy and mortality rate and cause of death. Epilepsia. 1974 Jun;15(2):191-201.

Annex 8 Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
2.1	Date of RMP: 20 Jan 2009	First version submitted to EMA with procedure X/48
3.0	Date of RMP: 11 Dec 2009	Updated in response to D120 questions in procedure X/48.
4.0	Date of RMP: 30 Mar 2010	Updated in response to D180 questions in procedure X/48.
5.a (reassigned from 5.0)*	Date of RMP: 20 Jun 2011	Converted into EMA template format, as well as updates due to availability of monotherapy study data and 8th PSUR (Additionally, two pages in the RMP [pages 3 and 73] were updated on 19 July 2011 to reflect the removal from the SmPC of a proposed change to the serious rash warning, requested by the EMA during validation of II/59.)
5.b (reassigned from 6.0)*	Date of RMP: 12 Aug 2011	Updated to reflect completion of pooled analysis of safety data on elderly subjects and submission of study E2090-E044-402, as well as to reclassify the previous missing information "use in the elderly" to an important potential risk.
5.c	Date of RMP: 11 Nov 2011	Updated in response to II/59 questions and to incorporate SmPC updates from variation IB/61 (DIHS & DRESS).
5.d	Date of RMP: 14 Dec 2011	Updated in response to questions on elderly variation (II/60)
6.1	Date of RMP: 15 Feb 2012	Updated to include a requirement for a drug utilisation analysis in response to the second preliminary assessment report on the elderly variation (II/60) dated 27 Jan 2012 and to correct an error in the comparative AE table in Section 5.2.1 "use in the elderly" by deleting the AE vomiting.
7.0	Date of RMP: 30 Mar 2012	Updated due to availability of results from Study 312 (RCT of zonisamide vs. placebo in paediatric adjunctive use) and pooled analysis of safety data on paediatric subjects.
8.0	Date of RMP: 16 Nov 2012	Updated in response to questions on the paediatrics indication (II/065).
9.0	Date of RMP: 15 Mar 2013	Updated in response to 2nd Request for Supplementary Information (RfSI) on paediatric extension of indication (II/65) to include strengthened warnings relating to use in paeds as well as additional risk minimisation measures (drug utilisation study, intensive monitoring, and educational materials).
10.0	Date of RMP: 14 Jun 2013	Updated in response to 3rd Request for Supplementary Information (RfSI) on paediatric extension of indication (II/65) to include updated strengthened warnings relating to use in paeds as well as updated additional risk minimisation measures (drug utilisation study, intensive monitoring, and educational materials).
11.0	Date of RMP: 16 Dec 2013	Updated in response to final assessment report for the paediatric extension of the indication (II/65), and re-mapped according to new template.
11.1	Date of RMP: 05 Mar 2014	Make corrections to the placement and description of the Drug Utilisation Study.

Version	Approval Date Procedure	Change
11.2	Date of RMP: 28 Apr 2014 Procedure: EMEA/H/C/000577/IB/0071 Date of approval: 22 May 2014	Updated in response to IB/71 assessment report.
12.0	Date of RMP: 12 Oct 2020	Transitioned RMP v11.2 to 12.0 in the new EU RMP template. Added 4 specific adverse reaction follow-up questionnaires (questions for reports of: kidney stones in children and adolescents; oligohidrosis, heat stroke, and hyperthermia in children and adolescents; metabolic acidosis in children and adolescents; and delayed physical and/or mental development in children and adolescents). Removed category 3 drug utilisation study from pharmacovigilance plan as study is complete.
12.1	Date of RMP: 04 Jan 2021	Updated in response to IB/0100 assessment report.

AE = adverse event, DIHS = Drug-induced Hypersensitivity Syndrome, DRESS = Drug Rash With Eosinophilia and Systemic Symptoms, EMA = European Medicines Agency, PSUR = Periodic Safety Update Report, RCT = randomised controlled trial, RfSI = Request for Supplementary Information, RMP = Risk Management Plan, SmPC = Summary of Product Characteristics.

* The format of this version number was changed retrospectively to indicate that this was a proposed version of the RMP undergoing assessment, rather than a final approved version.