EU Risk Management Plan for Zebinix® (eslicarbazepine acetate)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number: 23.0

Data lock point for this RMP: 21 October 2025

Date of final sign-off: 29 May 2026

Rationale for submitting an updated RMP: To include the final European Registry of Anti-epileptic Drugs in Pregnancy (EURAP) pregnancy exposure report.

Summary of significant changes in this RMP:

The RMP was updated according to the current RMP format provided by the European Medicines Agency (EMA) on 31 October 2018 (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2).

RMP Part	Major changes
Part II SI	Update of literature
Part II SIII	Update of exposure data
Part II SVII	Update of data and literature for safety concerns, and inclusion of EURAP report
Part II SVII.3	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"
Part II SVIII	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"
Part III.1	Inclusion of EURAP as another form of routine pharmacovigilance activity for the missing information of "Exposure during pregnancy"
Part III.2	Update of additional pharmacovigilance activities
Part V.1	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"
Part V.2	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"
Part V.3	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"
Part VI	Removal of all important potential and identified risks except "Cutaneous adverse reactions" and "Cardiovascular/cerebrovascular ischaemia"

Other RMP versions under evaluation:

No other RMPs are under evaluation by the EMA.

Details of the currently approved RMP:

Version number: 22.1

Approved with procedure: EMA/VR/0000275829

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QPPV name: Helena Gama

QPPV signature:

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Eslicarbazepine Acetate (ESL)
Pharmacotherapeutic group(s) (ATC Code)	N03AF04
Marketing Authorisation Holder (MAH)	Bial – Portela & Cª, S.A.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Zebinix®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: ESL [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, BIA 2-093, ESL] is a central nervous system (CNS)-active compound. It behaves as voltage-gated sodium and T-type voltage-gated calcium channels blocker and has anticonvulsant properties.
	Summary of mode of action: ESL was designed to constitute a third-generation, single-enantiomer member of the long established family of first-line dibenz[b,f]azepine anti-seizure medications (ASMs) represented by carbamazepine (CBZ, first-generation) and oxcarbazepine (OXC, second-generation). ESL shares the dibenzazepine nucleus containing a 5-carboxamide substitute with CBZ and OXC, but it is structurally different at the 10,11-position. This molecular variation results in differences in its metabolism. Unlike CBZ, ESL is not metabolised to CBZ-10,11-epoxide and is not susceptible to auto-induction of its own metabolism. Unlike OXC, which is metabolised to both eslicarbazepine (also called S-licarbazepine or BIA 2-194) and R-licarbazepine (also called BIA 2-195), ESL is a prodrug of eslicarbazepine, which is the drug entity responsible for the ESL pharmacological effect.
	Not applicable

Table Part I.1 – Product(s) Overview

Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: Monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy. Adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.
	Proposed: not applicable
Dosage in the EEA	Current: Zebinix may be taken as monotherapy or added to existing anticonvulsant therapy. The recommended starting dose is 400 mg once daily (QD) which should be increased to 800 mg QD after one or two weeks. Based on individual response, the dose may be increased to 1200 mg QD. Some patients on monotherapy regimen may benefit from a dose of 1600 mg QD. Dose adjustment might be needed for patients with renal impairment. Children above 6 years of age: The recommended starting dose is 10 mg/kg/day QD. Dosage should be increased in weekly or bi-weekly increments of 10 mg/kg/day up to 30 mg/kg/day, based on individual response. The maximum dose is 1200 mg QD. Children with a body weight of ≥60 kg: Children with a body weight of 60 kg or more should be given the same dose as for adults. The safety and efficacy of ESL in children aged 6 years and below has not yet been established. Route: Oral
	Proposed: not applicable
Pharmaceutical form(s) and strengths	Current: Tablet: 200 mg, 400 mg, 600 mg, 800 mg Oral suspension: 50 mg/mL
	Proposed: not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication:

ESL is indicated as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy and as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

Incidence:

Epilepsy affects more than 50 million adults and children worldwide and accounts for 0.7% of global population. Globally, in 2021, there were approximately 3.3 million new cases of active idiopathic epilepsy (age-standardised incidence rate 42.8 per 100,000) [GBD Epilepsy Collaborators 2025]. The global incidence of idiopathic epilepsy in the population aged 60 years and above has almost tripled (from 116,560.47 in 1990 to 339,711.09 cases in 2021), while age-standardized incidence rate has increased by 26.64% (from 25.04 per 100,000 in 1990 to 31.71 per 100,000 in 2021) [Xue et al. 2025]. Of the population affected, more than 80% of people with epilepsy live in low-income and middle-income countries [GBD Epilepsy Collaborators 2025]. A major contributor to the greater burden of epilepsy is the gap between the number of people with active epilepsy and those receiving treatment; 75% of patients with epilepsy in low-income and middle-income countries do not receive treatment at all [Espinosa-Jovel et al. 2018]. The burden of epilepsy is notably more severe in developing countries due to relatively poorer economic conditions, leading to higher morbidity and mortality rates than those observed in more affluent nations. This disparity is likely linked to inadequate healthcare funding, limited knowledge about epilepsy, restricted access to advanced treatments, including surgical interventions, and under-reporting due to stigmatisation of the disease in many countries [Ngugi et al. 2010, GBD Epilepsy Collaborators 2025]. The difference of prevalence and incidence among high-income countries and low- to middle-income countries is partly explained by some risk factors such as head trauma, CNS infections and perinatal injuries, which are more common in poor regions, particularly in rural areas [Sander 2003, Espinosa-Jovel et al. 2018].

The onset of epilepsy is most common at the extremes of life. The two highest peaks of incidence are in children and in the elderly (above 65 years) [Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders in 2025]. Epilepsy in childhood differs from epilepsy in adults especially by the occurrence of seizures in a structurally and functionally maturing brain, the occurrence of different types not seen in adults, and the occurrence of seizures as part of age dependent epilepsy syndromes. The incidence of epilepsy in children ranges from 41-187/100,000 with higher incidence reported in low-income countries, particularly in rural areas [Camfield and Camfield 2015].

Prevalence:

Prevalence estimates of epilepsy in the total population vary from 4 to 8 per 1000 subjects according to [Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders in 2025]. In 2021, there were 51.7 million people with epilepsy (idiopathic and secondary combined) globally, with an age-standardised prevalence of 658 per 100,000. Idiopathic epilepsy had an age-standardised prevalence of 307 per 100,000 globally, with 24.2 million prevalent cases, and secondary epilepsy had a global age-standardised prevalence of 350 per 100,000 [GBD Epilepsy Collaborators 2025].

However, this may be an underestimate as some studies in low-income countries suggest a prevalence of more than 10 per 1000. Prevalence estimates in low-income countries are generally higher than in high-income countries in the following order Africa >Latin America >North America >Asia ≈Europe [Wyllie et al. 2015].

The prevalence of epilepsy in children is consistently higher than the incidence, and ranges from 3.2 to 5.5/1000 in high-income countries and 3.6 to 44/1000 in low-income countries. The prevalence is also the highest in rural areas [Camfield and Camfield 2015].

Demographics of the population in the authorised indication – age and risk factors for the disease:

Risk factors for epilepsy include genetic factors and acquired brain damage, e.g. brain damage from prenatal or perinatal causes, congenital abnormalities or genetic conditions with associated brain malformations, severe head injury, stroke, infection of the CNS such as meningitis, encephalitis or neurocysticercosis, and brain tumours. Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of the cases globally. The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown. Some subtypes, e.g. reading epilepsy, are provoked by specific triggers, e.g. visual stimulation and reading. Unspecific factors that can provoke seizures are emotional stress, sleep deprivation, alcohol consumption, or febrile illness [Shorvon 2011, WHO Epilepsy 2024].

The incidence and prevalence of specific seizure types and epilepsy syndromes are less well documented in children. In population-based studies, there is a slight, but consistent, predominance of focal seizures compared with generalised seizures [Camfield and Camfield 2015]. Focal seizures affect up to ~61% of people with epilepsy. They are associated with an increased risk of injury and premature death than the general population [Ioannou et al. 2022]. Only about one third of children with epilepsy can be assigned to a specific epilepsy syndrome [Camfield and Camfield 2015].

The main existing treatment options:

ASMs are the cornerstone in the management of seizures, to achieve the ultimate goal of seizure-freedom with minimal side effects. Approximately 60% of newly diagnosed patients become seizure-free on the first ASM (monotherapy). An additional 10 to 20% may achieve freedom of seizures with polytherapy (adjunctive therapy). It is estimated that, even with polytherapy, about 30% of patients are not satisfactorily controlled, being referred to as "refractory" patients, with a significant burden in comorbidity and an increased risk of premature death [Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders in 2025, Ioannou et al. 2022]. In addition, many patients suffer from significant treatment-related adverse reactions. Newer ASMs have been developed with the aim of improving the benefit and/or risks of existing ASM therapy, and to improve quality of life. In fact, in addition to disease severity, as measured by seizure frequency, the patient's tolerability of ASMs and the presence of depression, stigma, and worry about new seizures are usually strongly associated with poor quality of life [St Louis et al. 2009, Hersi et al. 2022, Siebenbrodt et al. 2023].

For patients with seizures that are not controlled with these agents, alternative treatments include surgical resection of the seizure focus, ketogenic diets, vagus nerve stimulation, transcutaneous vagus nerve stimulation, implantable brain neurostimulation, trigeminal nerve stimulation, transcranial direct current stimulation, transcranial magnetic stimulation, disease-modifying therapies based on neuroinflammation and neuromodulation, drugs acting on the interleukin IL-1R1-TLR4 signaling pathway, prostanoids, gene therapy, and stem cell therapy [Liu et al. 2017, Riva et al. 2021].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In general, mortality rates are higher in people with chronic epilepsy compared with the general population age- and sex-matched cohorts. Overall, standardized mortality ratios (SMRs) range between 1.2 and 9.3 [Hitiris et al. 2007]. Studies have shown that it is greater in remote symptomatic epilepsy (ranging from 2.3 to 6.5) than in cryptogenic/idiopathic epilepsy (ranging from 1.3 to 1.8). The impact of epilepsy appears to be greatest early in the course of the seizure disorder and attenuates over time; excess mortality is concentrated in the early years after diagnosis. The relative impact, as measured by the SMR, appears greater in individuals under the age of 60 than in individuals above the age of 60 where the force of mortality, i.e. the population death rate, is greater [Berg et al. 2001].

Mortality is significantly higher in people with seizures of a structural or known (symptomatic) cause, as compared to unknown (i.e., cryptogenic) or idiopathic (no structural, metabolic cause, but presumed genetic) cause; mortality is higher in children than in adults, and lower in incidence than in prevalence studies [Trinka et al. 2023]. SMRs range from 1.6 to 3.0 in high-income countries [Thurman et al. 2017] to 19.8 in low- and middle-income countries [Levira et al. 2017]. Male patients, children and adolescents, as well as patients with lack of access to health facilities show a slightly increased SMR [Beghi et al. 2020, Trinka et al. 2023]. The most important immediate causes of mortality include sudden unexpected death in epilepsy (SUDEP), status epilepticus, injuries, and suicide. SUDEP among the general population of people with epilepsy reaches an incidence of 1.2 per 1000 person-years (95% confidence interval [CI], 0.9–1.5), with an incidence of 1.3 (95% CI, 0.9–1.8) in adults above 50 years of age and 1.1 (95% CI, 0.5–2.3) in children under the age of 16 years [Sveinsson et al. 2017].

Major risk factors for SUDEP include the persistence of seizures, nocturnal seizures, and generalised tonic-clonic seizures [Harden et al. 2017]. It is assumed that a significant proportion of SUDEP could be avoided with optimal care. There is some evidence suggesting a protective effect of adjunctive treatment with ASMs, especially polytherapy [Bosch et al. 2024].

Important co-morbidities:

Comorbidities in epilepsy are associated with adverse patients outcomes and decreased quality of life. Large-scale studies, surveying over million subjects from different countries, reported that between 26.8 and 84% of epilepsy patients had at least one comorbid medical condition (Seidenberg et al. 2009, Doherty et al. 2022). Different studies report that the most common comorbidities are psychiatric (up to 25%), particularly depression. Psychiatric disorders occur twice as often in people with epilepsy compared with the general population. Depression is the most common co-morbid condition that affects people with epilepsy, and it occurs 3-to 10-fold more often in those with uncontrolled epilepsy than in the general population. Depression affects up to 55% of patients with recurrent epilepsy and up to 9% of those with well-controlled seizures, although estimates vary according to the patient population studied, disease severity, and methodology used. Other psychiatric disorders with a high prevalence in epilepsy include other mood disorders, anxiety, schizophrenia and psychosis. Psychosis may occur both in direct and indirect relation to seizures, and suicide rates have also been shown to be increased versus the general population. Other comorbid conditions in patients with epilepsy may include bone health decreased and fractures, stroke, migraine and attention-deficit hyperactivity disorder [Kanner 2003, Gaitatzis et al. 2004, Seidenberg et al. 2009,Wyllie et al. 2015]. It is also likely that many people with epilepsy, particularly older adults, have more than one comorbid condition [Seidenberg et al. 2009]. Cross-sectional studies from country-wide healthcare registries provided insights into the burden of epilepsy-related comorbidities [Gaitatzis et al. 2004, Pantoja-Ruiz et al. 2025]. Neurodegenerative conditions, particularly dementias, Alzheimer's disease, and

Parkinson's disease, appeared more frequently in people with epilepsy. Upper gastrointestinal (GI) bleed occurred more frequently in epilepsy, as did cardio- and cerebrovascular disorders, fractures, pneumonia and chronic lung diseases, as well as diabetes [Gaitatzis et al. 2004, Pantoja-Ruiz et al. 2025].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage are summarised in the table below.

Table SII.1: Key safety findings

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Toxicity: *Single and repeat-dose toxicity:* (1) exposures achieved in animals lower than exposure in humans	(1) as a consequence no safety margins derived.
(2) dyslipidemia (increases in cholesterol in rats and dogs; increases in triglycerides in dogs)	(2) not confirmed by clinical data.
(3) thyroid follicular hyperplasia	(3) not confirmed by clinical data, but thyroid function changes considered relevant for monitoring.
Reproductive toxicity: (4) decreased female fertility at maternal or paternal toxic doses	(4) unknown
Developmental toxicity: (5) no direct teratogenic effects but secondary fetal toxicity at maternal toxic doses	(5) Considered relevant for monitoring; pregnancy data evaluation ongoing.
Nephrotoxicity: (6) in repeat-dose toxicological studies non-reversible nephropathy in rats, but not in mice or dogs	(6) As this effect was not observed in mice or dogs and it is consistent with an exacerbation of spontaneous chronic progressive nephropathy in this species, it is considered to be not relevant to humans.
Hepatotoxicity: (7) increased liver weights, hepatocellular hypertrophy/hepatocyte rarefaction in rats and mice	(7) The liver appeared to be the primary target organ in toxicity studies → liver disorder and hepatic enzymes increased are labeled as uncommon adverse drug reactions (ADRs) in the current Summary of Product Characteristics (SmPC).
Genotoxicity:	(8) no particular risk identified.

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
(8) sum of *in vitro* and *in vivo* tests did not identify particular risks	
Carcinogenicity: (9) increase in incidence of hepatocellular adenomas and carcinomas in mice	(9) not confirmed by clinical data.
General safety pharmacology: (1) cardiovascular (including potential for QT interval prolongation): no relevant effects in cardiovascular studies in dogs and *in vitro* in the human ether-à-go-go related gene and Purkinje fiber assays	(1) Cardiac safety is supported by a negative thorough QT study in which neither 1200 mg nor 2400 mg had any effects on electrocardiogram (ECG) intervals including QTc or ECG morphology.
(2) *in vitro* cardiac conduction study conducted to address ESL Food and Drug Administration (FDA)'s Postmarketing Request (PMR 4085-1). Half maximal inhibitory concentration (IC_{50}) for the inhibitory effect of eslicarbazepine on cloned human cardiac sodium channels (hNav1.5) peak sodium current was 1250 µM on hNav1.5 expressed in human embryonic kidney cells. The IC_{50} value corresponds to about 20-fold higher exposure levels than those observed for the unbound maximum concentration (C_{max}) at 1200 mg dose (Study 301).	(2) Prolongations in PR interval have been observed in clinical studies with ESL, therefore caution should be exercised in patients with medical conditions (e.g. low levels of thyroxine, cardiac conduction abnormalities), or when taking concomitant medicinal products known to be associated with PR prolongation.
(3) nervous system: sedation and abnormal gait, dose-limiting CNS adverse events (AEs) in toxicity studies	(3) ESL targets the CNS, and CNS ADRs such as dizziness and somnolence have been reported to be very common in clinical trials in epilepsy patients and are labeled as such.
(4) respiratory system: no relevant effects	(4) No relevant effects.
(5) diuresis and urinary electrolyte secretion: decreased in mice, increased in rats	(5) Hyponatraemia is a relevant ADR of ESL in humans and is in line with the ADR profile of other voltage-gated sodium channel blockers.
(6) gastrointestinal (GI): reduced GI transit in mice and decreased gastric emptying in mice and rats	(6) GI ADRs such as nausea and vomiting have been reported to be common in clinical trials and are labeled as such.
(7) "off-target" receptor screen: no relevant findings	(7) no particular risk identified.

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Mechanisms for drug-drug interactions: ESL is extensively converted to eslicarbazepine, which is mainly eliminated by glucuronidation (1) Cytochrome P450 (CYP)3A4 and uridine diphosphate-glucuronyl transferases Human liver microsomes: slight inhibitory effect on the activity of CYP3A4 (2) CYP2C19 Human liver microsomes: moderate inhibitory effect on CYP2C19-mediated tolbutamide 4-hydroxylation (3) Other enzymes and transporters Fresh human hepatocytes: no significant induction of CYP1A2 and Phase 2 enzymes involved in glucuronidation and sulphatation of 7-hydroxy-coumarin Eslicarbazepine is devoid of effects upon major G protein-coupled and ligand-gated receptors, enzymes and transporters .	(1) induction of CYP3A4 and uridine diphosphate-glucuronyl transferases with the potential to lower exposure to substrates that are mainly metabolised by these enzymes, e.g. simvastatin (addressed in current SmPC). (2) inhibition of CYP2C19 with the potential to increase exposure to substrates that are mainly metabolised by this enzyme, e.g. phenytoin (addressed in current SmPC). (3) relevant drug-drug interactions are considered unlikely for these enzymes and transporters.
Other toxicity-related information or data There is evidence that [^{14}C]-ESL passes into the milk of the lactating female mouse	Human data is lacking, and it is known from Trileptal® (OXC) use that eslicarbazepine passes into mother's milk (Trileptal®, Product Information). ESL should not be used during breast-feeding because a risk to the breast-fed child cannot be excluded (addressed in current SmPC).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The integrated safety database (ISDB) pools the data from all completed studies conducted by the MAH. The total number of patients exposed in the ESL clinical development program, covering all phases and all indications, is presented in Table SIII.1. At the cut-off date of 21 Oct 2025, ESL at any dose has been administered in 62 completed clinical studies and respective long-term extensions to 6401 subjects (Table SIII.1). Study BIA-2093-212 was not included in the exposure calculation since the patients did not swallow ESL. All ESL doses were given orally in the clinical studies, either as tablets or as a suspension.

Table SIII.1: Overview of total exposure in ESL clinical program (completed studies)

			Number of Subjects Treated		
Development Phase	**Subject Population**	**Number of Studies**	**ESL[a]**	**Placebo**	**Total[b]**
Phase I	Non-epileptic adults	37	961	273	1079[c]
Phase II	Adults/Children with partial-onset epilepsy[d]	4	270[e]	87	320
	Adults with PDN	1	485	96	557
	Adults with PHN	1	501	93	567
	Adults with migraine	1	274	136	410
	Adults with fibromyalgia	1	397	131	528
	Adults with bipolar disorder	3	174	51	199[f]
	Adults with epileptogenesis	1	61	62	123
Phase III	Adults/Children with partial-onset epilepsy	10	2649[g]	662	2938[h]
	Adults (Monotherapy)	4	863[g]	-	863
	Adults with PDN[i]	1	308	82	332
	Adults with PHN	1	219	60	240
Phase IV	Adults/Children with partial-onset epilepsy[k]	1	102	-	102
Total clinical studies[m]		62	6401	1733	7395

Development Phase	Subject Population	Number of Studies	Number of Subjects Treated ESL[a]	Placebo	Total[b]

DB-double-blind, ESL-eslicarbazepine acetate, ISDB-integrated safety database, OL-open-label, PDN-painful diabetic neuropathy, PHN-post-herpetic neuralgia.

a: Patients treated with ESL in the DB and OL phase are only counted once. Patients treated with placebo in the DB phase and continuing in the OL phase where they were treated with ESL are also counted in ESL group.

b: The total is not additive due to patients who were treated with placebo in DB parts of studies and ESL in OL parts of studies.

c: Numbers treated in Phase I studies are not additive due to Phase 1 study designs (e.g. cross-over).

d: A further 38 children 5-8 years of age tested ESL in Study BIA-2093-212 without swallowing, i.e. without actually receiving ESL, this exposure is not included.

e: 96 adults received ESL in Study -201; 31 children 2-17 years of age received ESL in Study -202. 120 children 6-16 years of age received ESL in -208.

f: The total is not cumulative due to 26 subjects who received placebo treatment in Studies -203 or -204 and then received ESL in Study -205.

g: Subjects from study 093-050 are not counted because these subjects participated in preceding Studies 093-045 or 093-046 and already received ESL there.

h: 380 adults received ESL in Study -301; 389 adults received ESL in -302; 232 adults received ESL in Study -303; 426 adults received ESL in study -304; 287 children 2-18 years of age received ESL in Study -305; 72 elderly patients received ESL in Study -401.

i: One patient was randomised to Placebo but received ESL in the DB part. This patient is counted under ESL.

k: A further 36 ESL exposed subjects in Study BIA-2093-451 without actually receiving ESL in this study are not included.

m: Without studies 212, 451; Numbers are not additive as studies may be included repeatedly for different indications.

Note: Phase I studies include BIA-2093-101, -102, -103, -104, -105, -106, -107, -108, -109, -110, -111, -112, -113, -114, -115, -116, -117, -118, -119, -120, -121, -122, -123, -124, -125, -126, -127, -128, -129, -130, -131, -132, SEP093-150, -153, -155, -160, - 453.
Phase II studies include BIA-2093-201, -202, -203, -204, -205, -206 (Part I-II), -207 (Part I-II), -208 (Part I-III), -209, -210, -211, -211/EXT, -213.
Phase III studies include 093-045, -046, -050, BIA-2093-301 (Part I - IV), -302 (Part I - III), -303 (Part I - II), -304 (Part I - III), -305 (Part I - V), -307 (Part I - II), -308 (Part I - II), -311, -311/EXT, -401.
Phase IV study: SEP093-701.

Source: ISDB

Exposure in Phase I studies

In the 37 Phase I studies, 961 non-epileptic adults received at least 1 dose of ESL (Table SIII.1). 518 subjects were exposed to single doses of ESL of up to 2400 mg, with the majority being exposed to at least 800 mg (Table SIII.2). 520 subjects received multiple doses of ESL up to 3600 mg QD; the majority was exposed to 800 or 1200 mg.

Table SIII.2Total patients exposed	154	518	125	520
≤200 mg	-	24	-	-

400 mg	-	46	-	12
600 mg	-	55	-	29
800 mg	-	318	-	140
900 mg	-	52	-	20
1200 mg	-	10	-	283
1600 mg		48	-	-
1800 mg	-	6	-	6
2000 mg		47	-	-
2400 mg	-	53	-	72
3000 mg QD	-	-	-	6
3600 mg QD	-	-	-	6

BID-twice daily, QD-once daily

Single-dose study data from Studies BIA-2093/-101, -103, -104, -105, -106, -109, -112, -113, -115, -117, -122, -123, -130, -131, -132, -153, -155, -160, -453.
Multiple-dose data from Studies BIA-2093/-102, -105, -106, -107, -108, -110, -111, -113, -114, -115, -116, -118, -119, -120, -121, -123, -124, -125, -126, -127, -128, -129 and -150.
Studies BIA-2093-105, -106, -113, -115 and -123 contained single and multiple dosing regimens and are therefore included in both columns.

Subjects were counted for each study period with different dose levels independently. BID dosing was counted as total daily dose.
For study periods with forced up-titration, subjects were counted with their maximum daily dose.

Note: Overall 961 patients were treated with ESL and 273 with Placebo in Phase 1 Studies.

Source: ISDB

Exposure in Phase II/III studies

Exposure data from double-blind (DB) and open-label (OL) (if applicable) Phase II/III trials are presented by duration and dose for the following indications:

- Partial onset seizure (POS), all patients (i.e. adults add-on and monotherapy and children)
- Adults with POS as add-on therapy
- Adults with POS as monotherapy
- Children with POS as add-on therapy
- Neuropathic pain (painful diabetic neuropathy and post-herpetic neuralgia)
- Bipolar disorder
- Migraine
- Fibromyalgia

Additionally, exposure data from DB and OL Phase II/III trials are summarised by age and gender and race/ethnicity for POS in all patients and in adults as add-on therapy, in adults as monotherapy, and in children. These data are not summarised for the indications neuropathic pain, bipolar disorder, migraine, or fibromyalgia as the primary efficacy endpoints were not met in any of the studies for these indications and the clinical development in these indications was ended.

Exposure to ESL is presented by duration in Table SIII.3. Over all indications, 5568 patients were treated with ESL with a cumulative exposure of 6022.1 patient-years for 5438 patients with data; approximately 90% of patients received up to 48 months of treatment.

For POS, 3210 paediatric and adult patients were treated with ESL with a cumulative exposure of 5193.6 patient-years for 3145 patients with data. By indication, 1886 adults received ESL as add-on therapy (cumulative exposure: 2331.1 patient-years for 1832 patients with data), 863 adults received ESL as monotherapy (cumulative exposure: 1962.6 patient-years for 858 patients with data), and 461 children received ESL as add-on therapy (cumulative exposure: 899.9 patient-years for 455 patients with data).

In the following indications for which clinical development was ended due to the small therapeutic effect of ESL, cumulative exposure was as follows.

- Neuropathic pain: 1513 patients; 630.8 patient-years for 1459 patients with data
- Bipolar disorder: 174 patients; 51.5 patient-years for 166 patients with data
- Migraine: 274 patients; 67.5 patient-years for 274 patients with data
- Fibromyalgia: 397 patients; 78.8 patient-years for 394 patients with data

Table SIII.3: Exposure by duration

Cumulative for all indications (person time)		
Duration of exposure	**Patients, n (%) (N=5568)**	**Person time (in years)**
Cumulative up to 1 month	708 (12.7)	26.4
Cumulative up to 3 months	1795 (32.2)	234.2
Cumulative up to 6 months	2632 (47.3)	502.0
Cumulative up to 12 months	3394 (61.0)	1066.0
Cumulative up to 18 months	4289 (77.0)	2162.7
Cumulative up to 24 months	4509 (81.0)	2555.6
Cumulative up to 36 months	4871 (87.5)	3438.2
Cumulative up to 48 months	5081 (91.3)	4164.2
Cumulative up to 60 months	5249 (94.3)	4912.0
Cumulative up to 72 months	5375 (96.5)	5599.2
Cumulative up to 84 months	5427 (97.5)	5932.8
Cumulative up to infinity	5438 (97.7)	6022.1
Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -203, -204, -205, -206 (Part I - II), -207 (Part I - II), -208 (Part I - III), -209, -210, 211 (Part I - EXT), -301 (Part I - IV), -302 (Part I - III), -303 (Part I - II), -304(Part I - III), -305 (Part I - V), -307 (Part I - II), -308 (Part I - II), -311 (Part I - EXT), -401, 093-701.		
Partial onset seizure (POS) (all patients)		
Duration of exposure	**Patients, n (%) (N=3210)**	**Person time (in years)**
Cumulative up to 1 month	298 (9.3)	10.1

Table SIII.3: Exposure by duration

Cumulative up to 3 months	567 (17.7)	58.4
Cumulative up to 6 months	844 (26.3)	158.5
Cumulative up to 12 months	1339 (41.7)	520.9
Cumulative up to 18 months	1996 (62.2)	1334.1
Cumulative up to 24 months	2216 (69.0)	1727.0
Cumulative up to 36 months	2578 (80.3)	2609.6
Cumulative up to 48 months	2788 (86.9)	3335.6
Cumulative up to 60 months	2956 (92.1)	4083.4
Cumulative up to 72 months	3082 (96.0)	4770.6
Cumulative up to 84 months	3134 (97.6)	5104.2
Cumulative up to infinity	3145 (98.0)	5193.6
Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -208 (Part I - III), 211 (Part I - EXT), 301 (Part I - IV), 302 (Part I - III), 303 (Part I - II), 304 (Part I - III), -305 (Part I - V), 311 (Part I - EXT), -401, and 093-701.		
Adults with POS as add-on therapy		
Duration of exposure	**Patients, n (%) (N=1886)**	**Person time (in years)**
Cumulative up to 1 month	205 (10.9)	6.6
Cumulative up to 3 months	364 (19.3)	34.6
Cumulative up to 6 months	554 (29.4)	102.9
Cumulative up to 12 months	897 (47.6)	351.5
Cumulative up to 18 months	1411 (74.8)	989.4
Cumulative up to 24 months	1500 (79.5)	1145.1
Cumulative up to 36 months	1652 (87.6)	1523.6
Cumulative up to 48 months	1745 (92.5)	1843.4
Cumulative up to 60 months	1786 (94.7)	2022.9
Cumulative up to 72 months	1795 (95.2)	2071.9
Cumulative up to 84 months	1822 (96.6)	2248.7
Cumulative up to infinity	1832 (97.1)	2331.1
Studies BIA-2093-201, -301 (Part I - IV), -302 (Part I & II), -303 (Part I & II), -304 (Part I - III), and –401, and 093-701		
Adults with POS as monotherapy		
Duration of exposure	**Patients, n (%) (N=863)**	**Person time (in years)**
Cumulative up to 1 month	76 (8.8)	2.7
Cumulative up to 3 months	140 (16.2)	13.3
Cumulative up to 6 months	202 (23.4)	35.5
Cumulative up to 12 months	294 (34.1)	101.7

Table SIII.3: Exposure by duration

Cumulative up to 18 months	361 (41.8)	183.4
Cumulative up to 24 months	443 (51.3)	331.9
Cumulative up to 36 months	580 (67.2)	654.7
Cumulative up to 48 months	663 (76.8)	941.1
Cumulative up to 60 months	731 (84.7)	1244.4
Cumulative up to 72 months	832 (96.4)	1798.8
Cumulative up to 84 months	857 (99.3)	1955.5
Cumulative up to infinity	858 (99.4)	1962.6
Studies 093-045, 093-046, 093-050, BIA-2093-311, -311/EXT.		
Children with POS as add-on therapy		
Duration of exposure	**Patients, n (%) (N=461)**	**Person time (in years)**
Cumulative up to 1 month	17 (3.7)	0.8
Cumulative up to 3 months	63 (13.7)	10.5
Cumulative up to 6 months	88 (19.1)	20.1
Cumulative up to 12 months	148 (32.1)	67.6
Cumulative up to 18 months	224 (48.6)	161.4
Cumulative up to 24 months	273 (59.2)	250.0
Cumulative up to 36 months	346 (75.1)	431.4
Cumulative up to 48 months	380 (82.4)	551.0
Cumulative up to 60 months	439 (95.2)	816.1
Cumulative up to 72 months	455 (98.7)	899.9
Cumulative up to infinity	455 (98.7)	899.9
Studies BIA-2093-202, -208 (Part I - III), -211 (Part I - EXT), -305 (Part I - V).		
Neuropathic pain		
Duration of exposure	**Patients, n (%) (N=1513)**	**Person time (in years)**
Cumulative up to 1 month	234 (15.5)	8.8
Cumulative up to 3 months	770 (50.9)	106.2
Cumulative up to 6 months	1003 (66.3)	184.5
Cumulative up to 12 months	1227 (81.1)	353.9
Cumulative up to 18 months	1459 (96.4)	630.8
Cumulative up to infinity	1459 (96.4)	630.8
Studies BIA-2093-206 (Part I & II), -207 (Part I & II), -307 (Part I & II), -308 (Part I & II).		
Bipolar disorder		

Table SIII.3: Exposure by duration

Duration of exposure	**Patients, n (%) (N=174)**	**Person time (in years)**
Cumulative up to 1 month	81 (46.6)	3.7
Cumulative up to 3 months	98 (56.3)	6.2
Cumulative up to 6 months	117 (67.2)	12.7
Cumulative up to 12 months	160 (92.0)	44.9
Cumulative up to 18 months	166 (95.4)	51.5
Cumulative up to infinity	166 (95.4)	51.5
Studies BIA-2093-203, -204, -205.		
Migraine		
Duration of exposure	**Patients, n (%) (N=274)**	**Person time (in years)**
Cumulative up to 1 month	21 (7.7)	1.0
Cumulative up to 3 months	44 (16.1)	4.9
Cumulative up to 6 months	274 (100.0)	67.5
Cumulative up to infinity	274 (100.0)	67.5
Studies BIA-2093-209.		
Fibromyalgia		
Duration of exposure	**Patients, n (%) (N=397)**	**Person time (in years)**
Cumulative up to 1 month	74 (18.6)	2.7
Cumulative up to 3 months	316 (79.6)	58.6
Cumulative up to 6 months	394 (99.2)	78.8
Cumulative up to infinity	394 (99.2)	78.8
Studies BIA-2093-210. ISDB-integrated safety database, POS-partial-onset seizures. Note: Cumulative exposure was calculated as the sum of all days any patient took a tablet (1 day for each day a patient took a tablet) for each time period divided by 365.25 to yield the patient-years. Erroneous records, where the end date is earlier than the start date, or exposure mistakes, where patients in the placebo arm received ESL during the DB part, have been ignored. Missing information has not been included. Source: ISDB		

Over all indications, most patients were treated with up to 1200 mg ESL. Details of exposure by ESL dose is presented in Table SIII.4 by indications.

Table SIII.4: Exposure by dose

Adults with POS as add-on therapy

Table SIII.4: Exposure by dose

Dose	Patients, n (%) (N=1886)	Person time (in years)
400 mg	741 (39.3)	155.1
600 mg	78 (4.1)	6.3
800 mg	1090 (57.8)	758.8
1000 mg	5 (0.3)	2.5
1200 mg	639 (33.9)	394.8
1600 mg	32 (1.7)	28.1
Titration regimen	45 (2.4)	1.8
Studies BIA-2093-201, -301 (Part I - IV), -302 (Part I & II), -303 (Part I & II), -304 (Part I - III), and –401, and 093-701		
Adults with POS as monotherapy		
Dose	**Patients, n (%) (N=863)**	**Person time (in years)**
400 mg	654 (75.8)	17.3
600 mg	249 (28.9)	4.8
800 mg	670 (77.6)	900.6
1200 mg	490 (56.8)	310.9
1600 mg	379 (43.9)	461.2
2000 mg	125 (14.5)	179.3
2400 mg	55 (6.4)	88.8
2800 mg	1 (0.1)	0.0
3200 mg	1 (0.1)	0.0
Studies 093-045, 093-046, 093-050, BIA-2093-311, -311/EXT.		
Children with POS as add-on therapy		
Dose	**Patients, n (%) (N=461)**	**Person time (in years)**
<400 mg	329 (71.4)	140.6
>400 - ≤800 mg	366 (79.4)	268.6
>800 - ≤1200 mg	262 (56.8)	474.0
>1200 mg	7 (1.5)	4.0
Studies BIA-2093-202, -208 (Part I - III), -211 (Part I - EXT), -305 (Part I - V).		
Neuropathic pain		
Dose	**Patients, n (%) (N=1513)**	**Person time (in years)**
400 mg	792 (52.3)	110.0
600 mg	378 (25.0)	27.9

Table SIII.4: Exposure by dose

800 mg	878 (58.0)	215.3
1000 mg	2 (0.1)	0.3
1200 mg	499 (33.0)	119.0
1400 mg	1 (0.1)	0.3
1600 mg	264 (17.4)	56.6
1800 mg	2 (0.1)	0.1
Studies BIA-2093-206 (Part I & II), -207 (Part I & II), -307 (Part I & II), -308 (Part I & II).		
Bipolar disorder		
Dose	**Patients, n (%) (N=174)**	**Person time (in years)**
300 mg	35 (20.1)	17.9
600 mg	70 (40.2)	1.7
800 mg	55 (31.6)	1.1
900 mg	102 (58.6)	16.2
1200 mg	60 (34.5)	1.5
1600 mg	47 (27.0)	1.2
1800 mg	55 (31.6)	11.6
2400 mg	23 (13.2)	0.7
Studies BIA-2093-203, -204, -205.		
Migraine		
Dose	**Patients, n (%) (N=274)**	**Person time (in years)**
400 mg	135 (49.3)	5.4
600 mg	139 (50.7)	5.5
800 mg	133 (48.5)	29.4
1200 mg	129 (47.1)	27.3
Studies BIA-2093-209.		
Fibromyalgia		
Dose	**Patients, n (%) (N=397)**	**Person time (in years)**
400 mg	264 (66.5)	29.7
600 mg	131 (33.0)	2.4
800 mg	130 (32.7)	24.9
1200 mg	123 (31.0)	21.8

Table SIII.4: Exposure by dose

Studies BIA-2093-210. ISDB-integrated safety database, POS-partial onset seizures. Note: For exposure by dose, the actual given dose within a defined time interval is used; this may or may not be the target dose. Source: ISDB

Exposure by age and gender

Exposure to ESL is presented by age and gender for patients with any indication and for patients with POS in Table SIII.5. Over all indications, approximately half of the patients treated with ESL were 18 to <50 years old with an exposure of about 3589 patient-years. Roughly 24% of subjects were between the age of 50 and <65 years (exposure: 1125.4 patient-years) and around 16% of subjects were ≥65 years (exposure: 408.3 patient-years). About 6% of patients treated with ESL were children, three quarters of whom were aged 6 to 17 years (exposure: 704.8 patient-years). Numbers of patients and exposure to ESL were generally comparable for male and female patients in all epilepsy indications in any age group.

Table SIII.5: Exposure by age group and gender

Cumulative for all indications				
Age group (years)	**Patients, n (%) (N=5568)**		**Person time (in years)**	
	Male	**Female**	**Male**	**Female**
0 - <2	12 (0.2)	11 (0.2)	10.7	10.9
2 - <6	50 (0.9)	44 (0.8)	108.7	64.9
6 – <12	97 (1.7)	76 (1.4)	178.3	145.8
12 - <18	82 (1.5)	83 (1.5)	193.9	186.8
18 - <50	1216 (21.8)	1578 (28.3)	1857.8	1730.9
50 - <65	541 (9.7)	767 (13.8)	582.3	543.1
65 - <75	281 (5.0)	298 (5.4)	146.3	154.6
75 - <85	119 (2.1)	159 (2.9)	48.3	48.1
≥85	12 (0.2)	12 (0.2)	7.9	3.1
Total	2410 (43.3)	3028 (54.4)	3134.1	2888.0
Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -203, -204, -205, -206 (Part I - II), -207 (Part I - II), -208 (Part I - III), -209, -210, 211 (Part I - EXT), -301 (Part I - IV), -302 (Part I - III), -303 (Part I - II), -304(Part I - III), -305 (Part I - V), -307 (Part I - II), -308 (Part I - II), -311 (Part I - EXT), -401, 093-701.				
Partial onset seizure (POS) (all patients)				
Age group (years)	**Patients, n (%) (N=3210)**		**Person time (in years)**	
	Male	**Female**	**Male**	**Female**
0 - <2	12 (0.4)	11 (0.3)	10.7	10.9
2 - <6	50 (1.6)	44 (1.4)	108.7	64.9

Table SIII.5: Exposure by age group and gender

6 – <12	97 (3.0)	76 (2.4)	178.3	145.8
12 - <18	82 (2.6)	83 (2.6)	193.9	186.8
18 - <50	1017 (31.7)	1052 (32.8)	1775.8	1578.2
50 - <65	245 (7.6)	234 (7.3)	441.1	360.5
65 - <75	63 (2.0)	49 (1.5)	69.4	47.4
75 - <85	15 (0.5)	14 (0.4)	8.4	7.9
≥85	1 (0.0)	NA	5.0	NA
Total	1582 (49.3)	1563 (48.7)	2791.2	2402.4
Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -208 (Part I - III), 211 (Part I - EXT), 301 (Part I - IV), 302 (Part I - III), 303 (Part I - II), 304 (Part I - III), -305 (Part I - V), 311 (Part I - EXT), -401, and 093-701.				
Adults with POS as add-on therapy				
Age group (years)	**Patients, n (%) (N=1886)**		**Person time (in years)**	
	Male	**Female**	**Male**	**Female**
18 - <50	682 (36.2)	742 (39.3)	970.4	907.5
50 - <65	155 (8.2)	149 (7.9)	221.1	171.2
65 - <75	42 (2.2)	38 (2.0)	27.1	23.5
75 - <85	12 (0.6)	12 (0.6)	5.1	5.2
≥85	NA	NA	NA	NA
Total	891 (47.2)	941 (49.9)	1223.8	1107.3
Studies BIA-2093-201, -301 (Part I - IV), -302 (Part I & II), -303 (Part I & II), -304 (Part I - III), and –401, and 093-701				
Adults with POS as monotherapy				
Age group (years)	**Patients, n (%) (N=863)**		**Person time (in years)**	
	Male	**Female**	**Male**	**Female**
18 - <50	335 (38.8)	310 (35.9)	805.4	670.8
50 - <65	90 (10.4)	85 (9.8)	220.0	189.4
65 - <75	21 (2.4)	11 (1.3)	42.2	24.0
75 - <85	3 (0.3)	2 (0.2)	3.3	2.7
≥85	1 (0.1)	NA	5.0	NA
Total	450 (52.1)	408 (47.3)	1075.8	886.7
Studies 093-045, 093-046, 093-050, BIA-2093-311, -311/EXT.				
Children with POS as add-on therapy				
Age group (years)	**Patients, n (%) (N=461)**		**Person time (in years)**	

Table SIII.5: Exposure by age group and gender

	Male	Female	Male	Female
0 - <2	12 (2.6)	11 (2.4)	10.7	10.9
2 - <6	50 (10.8)	44 (9.5)	108.7	64.9
6 – <12	97 (21.0)	76 (16.5)	178.3	145.8
12 - <18	82 (17.8)	83 (18.0)	193.9	186.8
Total	241 (52.3)	214 (46.4)	491.6	408.3
Studies BIA-2093-202, -208 (Part I - III), -211 (Part I - EXT), -305 (Part I - V). ISDB-integrated safety database, NA-not applicable, POS-partial onset seizures. Source: ISDB				

Exposure by race/ethnicity

Exposure to ESL is presented by ethnicity for patients with any indication and for patients with POS in Table SIII.6. Over all indications, the populations studied in the DB and OL Phase II/III trials were mainly Caucasian (approximately 85%), with roughly 4% of Hispanic ethnicity, roughly 5% Asian, and 2% of Black or African American, other, or multiple ethnicities.

Table SIII.6: Exposure by ethnic origin

Cumulative for all indications		
Race/Ethnicity	**Patients, n (%) (N=5568)**	**Person time (in years)**
White	4667 (83.8)	4983.6
Black or African American	113 (2.0)	132.4
Asian	329 (5.9)	402.8
Hispanic	195 (3.5)	269.2
Multiple	11 (0.2)	9.5
Other	122 (2.2)	224.4
Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -203, -204, -205, -206 (Part I - II), -207 (Part I - II), -208 (Part I - III), -209, -210, 211 (Part I - EXT), -301 (Part I - IV), -302 (Part I - III), -303 (Part I - II), -304(Part I - III), -305 (Part I - V), -307 (Part I - II), -308 (Part I - II), -311 (Part I - EXT), -401, 093-701.		
Partial onset seizure (POS) (all patients)		
Race/Ethnicity	**Patients, n (%) (N=3210)**	**Person time (in years)**
White	2528 (78.8)	4233.5
Black or African American	98 (3.1)	126.3
Asian	208 (6.5)	337.8
Hispanic	193 (6.0)	268.5
Multiple	11 (0.3)	9.5
Other	107 (3.3)	218.2

Table SIII.6: Exposure by ethnic origin

Studies 093-045, 093-046, 093-050, BIA-2093-201, -202, -208 (Part I - III), 211 (Part I - EXT), 301 (Part I - IV), 302 (Part I - III), 303 (Part I - II), 304 (Part I - III), -305 (Part I - V), 311 (Part I - EXT), -401, and 093-701.

Adults with POS as add-on therapy

Race/Ethnicity	Patients, n (%) (N=1886)	Person time (in years)
White	1383 (73.3)	1734.3
Black or African American	66 (3.5)	64.2
Asian	146 (7.7)	192.5
Hispanic	131 (6.9)	143.9
Multiple	8 (0.4)	3.1
Other	98 (5.2)	193.1

Studies BIA-2093-201, -301 (Part I - IV), -302 (Part I & II), -303 (Part I & II), -304 (Part I - III), and –401, and 093-701

Adults with POS as monotherapy

Race/Ethnicity	Patients, n (%) (N=863)	Person time (in years)
White	713 (82.6)	1673.5
Black or African American	30 (3.5)	56.1
Asian	42 (4.9)	77.8
Hispanic	62 (7.2)	124.5
Multiple	3 (0.3)	6.4
Other	8 (0.9)	24.3

Studies 093-045, 093-046, 093-050, BIA-2093-311, -311/EXT.

Children with POS as add-on therapy

Race/Ethnicity	Patients, n (%) (N=461)	Person time (in years)
White	432 (93.7)	825.7
Black or African American	2 (0.4)	6.0
Asian	20 (4.3)	67.4
Other	1 (0.2)	0.7

Studies BIA-2093-202, -208 (Part I - III), -211 (Part I - EXT), -305 (Part I - V).

ISDB-integrated safety database, POS-partial onset seizures.

Erroneous records, where the end date is earlier than the start date, or exposure mistakes, where patients in the placebo arm received ESL during the DB part, have been ignored.

Source: ISDB

In Study BIA-2093-213, 61 post-stroke patients were treated with 800 mg ESL per day and 62 post-stroke patients were treated with placebo for 30 days (5 patient-years), followed by a down-titration for 7 days. Patients were followed up for 18 months after randomisation.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table SIV.1: Effect of exclusion criteria across the clinical trial program

Exclusion criteria which will remain as contraindications	
Criteria	Implications for target population
(1) Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. CBZ, OXC) or to any of the excipients	Standard contraindication
(2) Known second or third degree atrioventricular (AV) block	Excluding risk for patients with known higher degree AV block

Table SIV.2: Exclusion criteria in pivotal and supporting studies

Study number	No. of patients exposed to ESL*	Age range (yrs)	Exclusion criteria
BIA-2093-201	96	19-61	• Patient with nervus vagus stimulation • Patient with primarily generalised seizures • Known progressive neurological disturbance • A history of status epilepticus within the past 3 months • Seizure of non-epileptic origin • Restricted legal competence and incapability to follow trial instructions • Major psychiatric disorders • Concurrent drug therapy with monoamine oxidase inhibitors or calcium channel blockers • Need of excluded concomitant medication • Use of OXC or CBZ during the last 6 months before the randomization visit • Known hypersensitivity to OXC or CBZ, or its metabolites • Abuse of alcohol, drugs or medications • History of relevant cardiac, renal, hepatic, endocrine, gastrointestinal, metabolic, hematologic or oncology disorders • Second- or third-degree AV block not corrected with a pacemaker • Relevant laboratory abnormalities (e.g. sodium <130 mmol/L, alanine (ALT) or aspartate (AST) transaminase >2.0 times the upper limit of normal, white blood cell (WBC) count <3000 cells/mm3) • Pregnancy, nursing or inadequate contraception in women of childbearing age (oral contraception should be combined with a barrier method) • Participation in other clinical trials within the last 2 months • History of non-compliance.
BIA-2093-301	300	18-76	*At Visit 1 (screening):* • Only simple partial seizures with no motor symptomatology (classified as A2-4 according to the International Classification of Epileptic Seizures). • Primarily generalised seizures. • Known rapid progressive neurological disorder. • History of status epilepticus or cluster seizures (i.e. 3 or more seizures within 30 minutes) within the 3 months prior to screening. • Seizures of psychogenic origin within the last 2 years. • History of schizophrenia or suicide attempt. • Currently on or with exposure to felbamate or OXC within one month of screening (Studies BIA-2093-301, -302, -303); currently treated with OXC (study -304). • Using benzodiazepines on more than an occasional basis (except when used chronically as ASM).
BIA-2093-302	295	18-69	
BIA-2093-303	165	17-68	
BIA-2093-304	426	16-71	

Study number	No. of patients exposed to ESL*	Age range (yrs)	Exclusion criteria
			• Previous use of ESL or participation in a clinical study with ESL. • Known hypersensitivity to CBZ, OXC, or chemically related substances. • History of abuse of alcohol, drugs or medications within the last 2 years. • Uncontrolled cardiac, renal, hepatic, endocrine, GI, metabolic, hematological or oncology disorder. • Second or third-degree AV blockade not corrected with a pacemaker. • Relevant clinical laboratory abnormalities (e.g. sodium <130 mmol/L, ALT or AST >2.0 times the upper limit of the normal, WBC count <3,000 cells/mm3). • Estimated creatinine clearance <50 mL/min (Studies BIA-2093-301, -302, -303), <60 mL/min (Study -304) [men: (140-age) x weight / serum creatinine x 72; women: (0.85) (140-age) x weight / serum creatinine x 72. Age in years, weight in kg, and serum creatinine in mg/dL]. • Pregnancy or nursing. • Participation in another drug clinical study within the last 2 months or received an investigational drug within 5 half-lives of this other product, whatever is longer. • Not ensured capability to perform the study. • Any other condition or circumstance that, in the opinion of the investigator, might compromise the patient's ability to comply with the study protocol. *At Visit 2 (randomization):* • Inadequate compliance to concomitant ASMs during the 8-week baseline period. • Inadequate completion of the study diary. • Any other condition or circumstance that, in the opinion of the investigator, might compromise the patient's ability to comply with the study protocol.
BIA-2093-311	401	18-85	*At Visit 1 (screening):* • History of pseudo-seizures. • Seizures occurring only in clusters. • History of absence, myoclonic, clonic, tonic, or atonic seizures. • Documented electroencephalogram within 12 months of Visit 1 suggestive of primarily generalized epilepsy. • History of status epilepticus within the 3 months prior to Visit 1. • Known progressive neurologic disorder (progressive brain disease, epilepsy secondary to progressive cerebral lesion) as assessed by magnetic resonance imaging or computer tomography.

Study number	No. of patients exposed to ESL*	Age range (yrs)	Exclusion criteria
			• Former or current use of any ASM, except for the use of a single ASM for a maximum duration of 2 weeks before Visit 1. • Previous regular use of ESL or CBZ (previous use as acute treatment for seizures in an emergency situation is not an exclusion criterion). • Using mono-amine oxidase inhibitors (MAOIs), tricyclic antidepressants, nefazodone, isoniazid, protease inhibitors or any other anti-retroviral agents (e.g. efavirez) that may raise the levels of carbamazepine controlled-release (CBZ-CR). • Known hypersensitivity to carboxamide derivatives or tricyclic antidepressants. • History of uncontrolled psychiatric illness or mood disorder requiring electro-convulsive or drug therapy within the previous 6 months, a history of suicide attempt, schizophrenia, chronic treatment with benzodiazepines (except short-acting benzodiazepines), or barbiturates. • Judged clinically to have a suicidal risk in the opinion of the investigator based upon a clinical interview and the Columbia Suicide-Severity Rating Scale (C-SSRS). • History of alcohol, drug, or medication abuse within the last 2 years. • Uncontrolled cardiac (including AV block and other clinically significant electrocardiographic abnormalities), renal, hepatic, endocrine, GI, metabolic, hematological, or oncology disorder. • History of bone marrow depression. • History of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). • Relevant clinical laboratory abnormalities (e.g. sodium <130 mmol/L, ALT or AST >2 x the upper limit of normal, WBC count <3000 cells/mm3) as measured at Visit 1. • Estimated glomerular filtration rate <60 mL/min/1.73 m2 as measured at Visit 1. • Patients of Asian ancestry who test positive for the presence of the human leukocyte antigen (HLA)-B*1502 allele. • Pregnancy or lactating. • Participation in other drug clinical trial within the last 2 months or having received an investigational medicinal product (IMP) within 5 half-lives of that IMP, whichever is longer. • Any other condition or circumstance that, in the opinion of the investigator, could compromise the patient's ability to comply with the study protocol. *At Visit 2 (randomization):*

Study number	No. of patients exposed to ESL*	Age range (yrs)	Exclusion criteria
			• Former or current use of any ASM, except for the use of a single ASM for a maximum duration of 2 weeks before Visit 1 and with a drug-free period of at least 5 days before Visit A1. Benzodiazepines are allowed for an epileptic indication and as rescue medication during the ≥5-day drug-free period. • Using prohibited medication. • Pregnancy. • Any other condition or circumstance that, in the opinion of the investigator, could compromise the patient's ability to comply with the study protocol.

* Double-blind period.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Ability to detect adverse reactions	**Limitation of trial program**	**Discussion of implications for target population**
Which are rare	6401 patients were exposed to ESL over the whole clinical trial program (completed clinical trials)	ADRs with a frequency greater than 1 in 2134 could be detected if there were no background incidence.
Due to prolonged exposure	More than 2000 patients were exposed to ESL for more than 1 year in clinical trials. (the longest exposure was over 18 years)	Although data on prolonged exposure for over 5 years are available, the profile of ADRs due to prolonged exposure is incomplete, in particular for rare ADRs due to prolonged exposure.
Due to cumulative effects	There are no findings in long-term toxicity studies that adverse effects may result from cumulative exposure to ESL or metabolites.	In a two-year carcinogenicity study in mice, an increase in the incidence of hepatocellular adenomas and carcinomas was seen at ESL doses ≥250 mg/kg/day in males and at 600 mg/kg/day in females. The mitogenic response associated with hepatomegaly appears to be restricted to rodents, and mice in particular, and therefore hepatomegaly-associated with mouse liver tumors are not considered relevant for human risk assessment.
Which have a long latency	More than 2000 patients were exposed to ESL for more than 1 year in clinical trials (the longest exposure was over 18 years).	The probability that ADRs with a long latency period could have been detected during clinical trials with ESL is low, in particular for rare ADRs that have a long latency.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.3: 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.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities:	Not included in the clinical development programme.
• Patients with hepatic impairment	Mild hepatic impairment: 0 subjects exposed to ESL Moderate hepatic impairment: 9 subjects exposed to multiple doses of 800 mg ESL Severe hepatic impairment: 0
• Patients with renal impairment	Mild renal impairment: 8 subjects exposed to a single dose of 800 mg ESL Moderate renal impairment: 8 subjects exposed to a single dose of 800 mg ESL Severe renal impairment: 8 subjects exposed to a single dose of 800 mg ESL End-stage renal disease: 8 subjects exposed to a single dose of 800 mg ESL
• Patients with cardiovascular impairment	Not included in the clinical development programme.
• Immunocompromised patients	Not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	Subjects of different ethnic origin were included in clinical trials. No data on comparative efficacy or safety in subpopulations of different racial and/or ethnic origin are available.
Subpopulations carrying relevant genetic polymorphisms	For some inherited idiopathic human epilepsies (see e.g. Chapter 4, Table 4.1 in [Wyllie et al. 2015], specific mutations in ion channel subunits were identified. No data on comparative efficacy or safety in subpopulations based on genetic causes are available.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

Cumulative patient exposure to marketed ESL was estimated on the basis of world-wide ex-factory sales.

For estimation of patient exposure it was assumed that the ex-factory amounts delivered were entirely dispensed and actually all administered, and were used at the dosage regimen of 1 tablet per day, regardless of dose strength as recommended in the ESL SmPC. Because ESL is intended for long-term therapy, exposure is calculated in patient-months (units divided by 30) and patient-years, rather than in number of treated patients. The cumulative exposure data since marketing authorisation, issued below, will not match with the table SV.1 because it was only possible to retrieve exposure by country since 2014.10.22 for this analysis.

SV.1.2 Exposure

On the basis of these assumptions, the estimated patient exposure from the time of marketing authorization until the data lock point (DLP) is a total of 12,117,960 patient-months, corresponding to 1,009,830 patient-years.

Table SV.1: Cumulative patient exposure by country in the interval from 2014.10.22 to 2025.10.21

Country	Units (1 unit = 1 tablet)	Patient exposure (in months)
ALBANIA	[redacted]	[redacted]
ANGOLA	[redacted]	[redacted]
AUSTRIA	[redacted]	[redacted]
CANADA	[redacted]	[redacted]
CHINA	[redacted]	[redacted]
CYPRUS	[redacted]	[redacted]
CZECH REPUBLIC	[redacted]	[redacted]
DENMARK	[redacted]	[redacted]
DOMINICAN REPUBLIC	[redacted]	[redacted]
EL SALVADOR	[redacted]	[redacted]
FINLAND	[redacted]	[redacted]
FRANCE	[redacted]	[redacted]
FRANCE ISLANDS	[redacted]	[redacted]
GERMANY	[redacted]	[redacted]
GREECE	[redacted]	[redacted]
GUATEMALA	[redacted]	[redacted]
HONDURAS	[redacted]	[redacted]
ICELAND	[redacted]	[redacted]

Country	Units (1 unit = 1 tablet)	Patient exposure (in months)
IRELAND	[redacted]	[redacted]
ISRAEL	[redacted]	[redacted]
ITALY	[redacted]	[redacted]
KOREA, REPUBLIC OF	[redacted]	[redacted]
LEBANON	[redacted]	[redacted]
LUXEMBURG	[redacted]	[redacted]
MALTA	[redacted]	[redacted]
MOLDOVA, REPUBLIC OF	[redacted]	[redacted]
MOZAMBIQUE	[redacted]	[redacted]
NORWAY	[redacted]	[redacted]
PANAMA	[redacted]	[redacted]
PORTUGAL	[redacted]	[redacted]
RUSSIA	[redacted]	[redacted]
SAN MARINO	[redacted]	[redacted]
SAUDI ARABIA	[redacted]	[redacted]
SLOVAKIA	[redacted]	[redacted]
SPAIN	[redacted]	[redacted]
SWEDEN	[redacted]	[redacted]
SWITZERLAND	[redacted]	[redacted]
UNITED ARAB EMIRATES	[redacted]	[redacted]
UNITED KINGDOM	[redacted]	[redacted]
UNITED STATES OF AMERICA	[redacted]	[redacted]
TOTAL	**323595217**	**10786507**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

In vitro assays demonstrated that ESL and its metabolites do not interact with receptor systems likely to cause concern regarding dependency, abuse liability, or addiction.

Two dose finding studies (for ESL and diazepam) and a study on the dependence potential in mice were conducted. The data does not give evidence of a potential for abuse liability of ESL and its metabolites.

The abuse and dependence potential of ESL was evaluated in a clinical study (SEP093-453) which concluded that ESL was not associated with physical dependence based on maximum change from steady-state baseline in total score of the 34-item physician withdrawal checklist (PWC-34). The treatment-emergent adverse events (TEAEs) that occurred after abrupt discontinuation of ESL were mild or moderate and consistent with the known safety profile of ESL. No marked differences in cognitive and psychomotor effects were observed between the ESL discontinuation and placebo groups.

Furthermore, no cases pointing to misuse for illegal purposes have been reported.

In conclusion, we do not consider that there is a potential for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The identified risks not classified as important and their frequency are reflected in the current SmPC of Zebinix®. Review of the data up to 21 October 2025 for this RMP did not reveal a particular new risk.

The risks that have been identified for ESL are mainly class-based, dose-dependent undesirable effects. The most common adverse reactions reported, in placebo-controlled adjunctive therapy studies with adult epileptic patients and in an active controlled monotherapy study comparing ESL with CBZ-CR, were dizziness, somnolence, headache, and nausea.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

At the time of authorisation, following safety concerns had been defined.

- Identified Risks
    - Hyponatraemia
    - Cutaneous adverse reactions
- Potential Risks
    - Thyroid function changes
    - International normalised ratio (INR) and activated partial thromboplastin time (aPTT) increase
    - Cardiovascular/cerebrovascular ischaemia
    - Potential for suicidality as anti-epileptic drug
- Missing information
    - Exposure during pregnancy
    - Paediatric population
    - Elderly population
    - Interactions: inducing properties of ESL on:
        - CYP3A4
        - Carbamazepine

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Since marketing authorisation, the following safety concerns have been added in previous RMP versions:

- Bone metabolism disorders, including osteocalcin increased, decreased bone mineral density, osteopenia, osteoporosis, and fracture added as an important potential risk (RMP version 10.0).

- Terms 'vasculitis', 'leukocytoclastic vasculitis', and 'purpura' added to the important identified risk cutaneous adverse reactions (RMP version 10.0).
- Long term effects in children development added as missing information (RMP version 17.0), which was then renamed to 'Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children' (RMP version 18.0).

The following safety concerns have been reclassified in previous RMP versions since marketing authorisation:

- Inducing properties of ESL on CYP3A4 and CBZ removed as important missing information (RMP version 6.0).
  Information from studies BIA-2093-124 and BIA-2093-129 resolved issue of the inducing properties of ESL on CYP3A4 and CBZ.
- Age group 2-18 years was removed from missing information. Paediatric population maintained as missing information for children below 2 years of age (RMP version 14.0).
  This update reflected the completed Paediatric Investigation Plan (PIP) studies BIA-2093-202 [redacted] BIA-2093-212, BIA-2093-305 and BIA-2093-208 (EMA/PE/0000248063). ESL continues under clinical development for use in children below 2 years of age.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The important identified risks discussed in this section are:

- Cutaneous adverse reactions

The important potential risks are:

- Cardiovascular/cerebrovascular ischaemia

Topics referring to missing information are:

- Exposure during pregnancy
- Paediatric population (<2 years of age)
- Elderly population
- Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

For each important identified risk, the available data for the risk characterisation is presented in the order described below and includes subpopulations. For each important potential risk, the CT data for risk characterisation is presented for the whole population only.

Clinical trials

Incidences of TEAEs and ADRs from completed clinical trials are reported for ESL – and (if applicable) placebo-treated patients.

a. Indication epilepsy / all studies

- Studies 093-045, 046, 050, 701; BIA-2093-201, 202, 208 (Part I - III), 211 (Part I - EXT), 301 (Part I - IV), 302 (Part I - III), 303 (Part I - II), 304 (Part I - III), 305 (Part I - V), 311 (Part I - EXT), 401; N=3196, includes 491 patients <18 years, 2562 patients 18-64 years and 143 patients ≥65 years

b. Adult patients with epilepsy treated with ESL as adjunctive therapy of POS

- DB placebo-controlled studies, i.e. Studies BIA-2093-201, 301, 302, 303, 304, DB part (Part I); ESL N=1282, Placebo N=559
- OL uncontrolled long-term extensions, i.e. Studies 093-701; BIA-2093-301 (Part II - IV), 302 (Part II - III), 303 (Part II), 304 (Part II - III), 401; N=1488

c. Adult patients with epilepsy treated with ESL as monotherapy of POS

- DB CBZ-controlled studies, i.e. Studies 093-045, 093-046, BIA-2093-311; CBZ N=412, ESL N=766;
- OL extensions, i.e. Studies 093-050, BIA-2093-311/EXT; N=481

d. Elderly patients with epilepsy - subgroup

- DB studies, i.e. Studies 093-045, 093-046; BIA-2093-301 (Part I), -302 (Part I), -303 (Part I), -304 (Part I), -311; N=50
- OL extensions, i.e. Studies 093-050, 701; BIA-2093-301 (Part II - IV), 302 (Part II - III), 303 (Part II), 304 (Part II – III), 311 (EXT Part), 401; N=117

e. Children with adjunctive treatment of POS

- DB placebo-controlled studies, i.e. Studies BIA-2093-202, -208 (Part I), -305 (Part I); ESL N=269, Placebo N=189
- OL uncontrolled long-term extension, i.e. Studies BIA-2093-211 (Part I - EXT Part), -208 (Part II - III) and -305 (Part II - V); N=395

f. Adults with neuropathic pain

- DB placebo-controlled studies, i.e. Studies BIA-2093-206 (Part I), -207 (Part I), -307 (Part I), and -308 (Part I); ESL N=1365, Placebo N=331
- OL uncontrolled long-term extensions, i.e. Studies BIA-2093-206 (Part II), -207 (Part II), -307 (Part II), and -308 (Part II); N=623

Furthermore, seriousness, outcome and severity are presented for

a. indication epilepsy / all studies, and

b. adult patients with neuropathic pain, if applicable.

AEs, demographic, and exposure data from the individual clinical trials were pooled in an ISDB. The ISDB includes Sunovion-sponsored studies. AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version current at the time of study start or database lock, the coded Lower Level Terms from the individual studies were merged with the actual MedDRA version to get the actual MedDRA hierarchy. 95% CIs for the incidence of AEs were calculated according to Clopper and Pearson. For seriousness, severity and relatedness, a worst-case scenario for imputation of missing values is implemented.

Post-marketing data

For suspected ADRs (implied causality) from spontaneous reporting (and serious solicited events) as retrieved from the MAH's global safety database (Argus Safety™) cumulative frequencies are given. Only valid cases (valid individual case safety reports) are considered.

SVII.3.1. Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk: cutaneous adverse reactions

Potential mechanisms:

There is growing evidence that the most common drug eruptions and many severe ones arise as a result of immunological mechanisms [Weiss and Adkinson 1988; Del Pozzo-Magaña and Liy-Wong 2022].

Evidence source(s) and strength of evidence:

Skin rash may affect 1 to 10 ESL users in 100.

Hypersensitivity (allergic reactions) may affect 1 to 10 ESL users in 1000.

Very rare but serious skin side effects that involve mucous membranes, large areas of the skin, blisters, bloodshot skin may occur with treatment of the chemically related ASMs CBZ and OXC and it cannot be excluded to also occur with ESL. Patients with certain gene variants are more likely to develop serious skin side effects to CBZ than those without these gene variants.

Characterisation of the risk:

Epidemiological data and background information

Cutaneous ADRs are among the most common types of adverse reactions to drug therapy. The incidence of cutaneous reactions ranges between 1 and 3% of hospitalised patients in developed countries, whereas in developing countries some studies peg it to 2-5% of the in-patients [Nayak and Acharjya 2008]. Overall, ASMs are among the most common cause of cutaneous adverse reactions, observed in about 3% of users of ASMs [Gangemi and Valletta 2017]. Among these drugs, the risk is particularly high for phenytoin, phenobarbital, CBZ and OXC (aromatic compounds), and the incidence of cutaneous adverse reactions reaches about 10% in CBZ users [Kaniwa and Saito 2013]. More rarely, anti-epileptics can cause severe and life-threatening cutaneous reactions like Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are considered to be different levels of severity of one and the same disease entity, which shares the same cause and underlying mechanism [Mockenhaupt 2017]. Based on International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) data [Mockenhaupt 2017], the SJS/TEN incidence is 1–2 cases per 1,000,000 inhabitants per year. Another estimated incidence of these reactions is 1.5–8.3 cases per 1,000,000 person-years [Borrelli et al. 2018]. Also, drug reaction with eosinophilia and systemic symptoms (DRESS), another serious cutaneous adverse reaction, can present itself with cutaneous signs and symptoms such as exanthema, rash associated with eosinophilia, visceral involvement (often the liver), high fever, atypical lymphocytes, mild mucosal involvement, and lymphadenopathy [Ngugi et al. 2010]. HLA-A*31:01 is reported as being strongly associated with CBZ-induced DRESS in Europeans and also in Chinese [Sander 2003].

The incidence of DRESS is estimated between 1 in 1000 and 1 in 10,000 depending on the drug culprit with a median (interquartile range) age at diagnosis of 50 (31-64) years; in the paediatric population a mean age at diagnosis of DRESS ranging from 9 to 10 years was reported. The typical latency period is

2-6 weeks from drug exposure to DRESS onset. Reported mortality rates range from 1.2% to 6.1%, with hepatic necrosis as the leading cause of death (review in [Wei et al. 2023]).

Clinical trial data

Incidence

All PTs in the SOC 'skin and subcutaneous tissue disorders', and the PTs 'drug hypersensitivity' and 'hypersensitivity' from the SOC 'immune system disorders' are classified as cutaneous. Incidences are given in percentages together with their 95% CIs for all cutaneous TEAEs and ADRs (=TEAEs assessed as at least possibly related by the investigator) in the ESL groups and, if applicable, in the placebo or CBZ groups. Individual cutaneous ADRs are specified if the respective MedDRA PT was at least common (incidence ≥1%) in any treatment group.

a. Indication epilepsy / all studies
   - TEAEs: 10.0 (9.0; 11.1)
   - ADRs overall: 3.9 (3.2; 4.6)
   - ADRs with incidence ≥1%: 'rash' 1.2 (0.9; 1.7)

b. Adult patients with epilepsy treated with ESL as adjunctive therapy of POS
   - DB placebo-controlled studies:
     - TEAEs: ESL 5.6 (4.4; 7.0); placebo 5.9 (4.1; 8.2)
     - ADRs overall: ESL 3.0 (2.1; 4.0); placebo 2.1 (1.1; 3.7)
     - ADRs with incidence ≥1%: ESL 'rash' 1.1 (0.6; 1.8)
   - OL studies:
     - TEAEs: 6.0 (4.9; 7.4)
     - ADRs overall: 1.7 (1.1; 2.5)
     - ADRs with incidence ≥1%: none

c. Adult patients with epilepsy treated with ESL as monotherapy of POS
   - DB CBZ-controlled studies:
     - TEAEs: ESL 11.4 (9.2; 13.8); CBZ 18.0 (14.4; 22.0)
     - ADRs overall: ESL 6.1 (4.5; 8.1); CBZ 10.2 (7.4; 13.5)
     - ADRs with incidence ≥1%: ESL 'rash' 1.8 (1.0; 3.0); CBZ 'hypersensitivity' 1.2 (0.4; 2.8), 'dermatitis allergic' 2.2 (1.0; 4.1), 'rash' 2.2 (1.0; 4.1), 'pruritus' 1.0 (0.3; 2.5)
   - OL extension:
     - TEAEs: 7.1 (4.9; 9.7)
     - ADRs overall: 0.8 (0.2; 2.1)
     - ADRs with incidence ≥1%: none

d. Elderly patients with epilepsy
   - DB

- TEAEs: 12.0 (4.5; 24.3)
- ADRs overall: 6.0 (1.3; 16.5)
- ADRs with incidence ≥1%: 'erythema' 2.0 (0.1; 10.6), 'pruritus' 2.0 (0.1; 10.6), 'skin reaction' 2.0 (0.1; 10.6)

- OL
  - TEAEs: 7.7 (3.6; 14.1)
  - ADRs overall: 1.7 (0.2; 6.0)
  - ADRs with incidence ≥1%: none

e. Children with adjunctive treatment of POS
- DB placebo-controlled studies:
  - TEAEs: ESL 8.6 (5.5; 12.6); placebo 6.9 (3.7; 11.5)
  - ADRs overall: ESL 2.6 (1.1; 5.3); placebo 1.1 (0.1; 3.8)
  - ADRs with incidence ≥1%: none
- OL studies:
  - TEAEs: 7.6 (5.2; 10.7)
  - ADRs overall: 1.3 (0.4; 2.9)
  - ADRs with incidence ≥1%: none

f. Adult patients with neuropathic pain
- DB placebo-controlled studies:
  - TEAEs: ESL 7.4 (6.1; 8.9); placebo 2.7 (1.3; 5.1)
  - ADRs overall: ESL 5.2 (4.1; 6.5); placebo 1.5 (0.5; 3.5)
  - ADRs with incidence ≥1%: ESL 'rash' 2.1 (1.4; 3.0), 'pruritus' 1.4 (0.8; 2.2)
- OL studies:
  - TEAEs: 5.8 (4.1; 7.9)
  - ADRs overall: 3.0 (1.8; 4.7)
  - ADRs with incidence ≥1%: none

Overall, rash was the most commonly reported cutaneous TEAE and ADR across all studies.

Seriousness

a. Indication epilepsy / all studies
  - Serious TEAEs: a total of 13; 'angioedema' (1), 'dermatitis' (1), 'drug reaction with eosinophilia and systemic symptoms' (1), 'leukocytoklastic vasculitis' (1), 'night sweats' (1), 'rash' (2), 'rash pruritic' (1), 'rash vesicular' (1), 'skin mass' (1), 'urticaria' (2), and 'vascular purpura' (1)

b. Adult patients with neuropathic pain
   - DB placebo-controlled studies:
     - Serious TEAEs: a total of 3; 'drug hypersensitivity', 'dermatitis allergic', and 'rash' (1 each)
   - OL studies:
     - Serious TEAEs: 'diabetic foot' (1)

Outcome (% of all patients exposed to ESL)

a. Indication epilepsy / all studies
   - recovered (8.0), recovered with sequelae (0.3), ongoing (2.6), unknown (0.3), recovering (0.1); no deaths

b. Adult patients with neuropathic pain
   - DB placebo-controlled studies: recovered (6.2), recovered with sequelae (0.1), ongoing (0.8), unknown (0.1), recovering (0.4); no deaths
   - OL studies: recovered (4.5), recovered with sequelae (0.5), ongoing (0.8), unknown (0.2); no deaths

Severity (% of all ESL exposed patients, maximum severity in the individual patient)

a. Indication epilepsy / all studies
   - TEAEs: mild (6.4), moderate (3.1), severe (0.5)

b. Adult patients with neuropathic pain
   - DB placebo-controlled studies:
     - TEAEs: mild (3.3), moderate (2.9), severe (1.2)
   - OL studies:
     - TEAEs: mild (2.9), moderate (2.4), severe (0.5)

Post-marketing data

Up to 21 October 2025, the cumulative number of suspected ADRs in the SOC 'skin and subcutaneous tissue disorder' from spontaneous reporting is 622 (187 serious, 435 non-serious); there are 11 serious solicited events. Most commonly reported events (PT) are: 'rash' (198), 'pruritus' (66), and 'urticaria' (31). The severe cutaneous adverse reactions (SCARs), 'drug reaction with eosinophilia and systemic symptoms' (DRESS) (32) and 'Stevens-Johnson syndrome' (SJS) (13)/ 'toxic epidermal necrolysis' (TEN) (3), and also 'angioedema' (10) were identified from post-marketing data and labelled as ADRs to ESL with unknown frequency.

Risk factors and risk groups:

Such an association is suspected with OXC [Liu et al. 2018], which is chemically and pharmacokinetically more closely related to ESL.

More than 200 medications, among them CBZ and other anti convulsants, have been associated with the occurrence of SJS or TEN. Risk is usually restricted to the first weeks of drug intake. Other conditions causing SJS or TEN are infections and malignancies.

Several risk factors for drug-hypersensitivity have been identified: drug related aspects (hapten/pro-hapten reaction concept), type of treatment regimen (intermittent>repeated>continuous), dose, host-related: gender (female>male), and ethnicity.

HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing SCARs known as SJS when treated with CBZ.

The chemical structure of ESL is similar to that of CBZ, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with ESL. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these patients should be screened for this allele before starting treatment with CBZ or chemically-related compounds. If patients of these origins are tested positive for HLA-B*1502 allele, the use of ESL may be considered if the benefits are thought to exceed risks.

Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.

The prevalence of the HLA-B*1502 allele is negligible in sampled individuals of European descent, African, Hispanic, and in Japanese and Koreans (<1%).

Some data that suggest that HLA-A*3101 is associated with an increased risk of CBZ induced cutaneous ADRs including SJS, TEN, DRESS, or less severe acute generalised exanthematous pustulosis and maculopapular rash in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for CBZ-induced cutaneous reactions (mostly less severe) from 5.0% in the general population to 26.0% among patients of European ancestry, whereas its absence may reduce the risk from 5.0 to 3.8%. There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting CBZ or chemically-related compounds treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of CBZ or chemically-related compounds may be considered if the benefits are thought to exceed the risks.

Preventability:

By warning physicians and patients of the potential for this risk in the SmPC, they can monitor for its occurrence and potentially catch an event before it becomes serious. In addition, by collecting further data on cutaneous reactions, the MAH can better understand its true frequency in patients treated with ESL and provide better guidance to physicians and patients. By genotyping patients experiencing SJS/TEN for different HLA subsets, it is possible to closer determine the association measures in comparison to patients in which these alleles are not present. The MAH acknowledges that it is not possible to assure genotyping analysis for the targeted patients, as it depends on the patient's willingness to be subjected to this analysis. HLA analysis is not part of the standard of care for SCARs and is therefore voluntary, thus the MAH cannot request the performance of genotyping, which would be interfering with the prescriber's clinical practice. For this reason, the role of the MAH can be that of collecting information if it exists, and giving recommendations, which will be at the patient's and physician's discretion.

Impact on the risk-benefit balance of the product:

The low incidence of cutaneous adverse reactions related to ESL does not affect the potential benefit of the product. Risk-benefit balance remains positive.

Public health impact:

The potential impact in public health is considered low due to the low incidence of cutaneous adverse reaction related to ESL.

SVII.3.1.2 Important potential risk: cardiovascular/cerebrovascular ischaemia

Potential mechanisms:

Some of the older anticonvulsants (i.e. CBZ, phenobarbital, phenytoin, and primidone) have been associated with metabolic changes that may contribute to cardiovascular risk. The mechanism underlying this association might reside in the interaction between these medications and CYP system activity. Several investigations have shown that patients treated with anticonvulsants that highly induce CYP enzyme system activity, such as phenytoin, CBZ, or phenobarbital, experienced elevated levels of total cholesterol and most of the various lipid fractions, including low-density lipoprotein cholesterol and serum triglycerides as well as increases in serum lipoprotein(a) and serum homocysteine [Patorno et al. 2013].

In a multicentre, retrospective, observational, non-interventional, real-life study comparing patients treated with CYP inducer vs. ESL plus non-inducer ASMs [Serrano-Castro et al 2017], the use of CYP inducer ASMs was associated with an increase in carotid intima-media thickness as compared with ESL and other non-inducer ASMs; this increase was significant in men, but not in women. CYP inducers (inducers group, 90 patient) were defined as patients with epilepsy on treatment for ≥2 years with ≥1 of the following ASMs: CBZ, phenobarbital, phenytoin, primidone, topiramate, OXC or felbamate. Non-CYP inducers (non-inducers group, 73 patients) were defined as patients treated with ESL for ≥2 years who have not received in the previous two years any of the ASMs in the inducer group. There were imbalances between groups, in the inducer group duration of epilepsy was longer, dyslipidaemia and use lipid-lowering drugs more prevalent, whereas the number of previous ASMs was higher in the non-inducer group.

Evidence source(s) and strength of evidence:

Some of the older anticonvulsants (i.e. CBZ, phenobarbital, phenytoin, and primidone) have been associated with metabolic changes that may contribute to cardiovascular risk. At present, available data does not indicate that there is an increased cardiovascular or cerebrovascular risk in ESL users.

Characterisation of the risk:

Epidemiological data and background information

Cardiovascular diseases (CVDs) are the leading cause of death globally, with an estimated 19.8 million people dying from CVDs in 2022, representing approximately 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke. Over three quarters of CVD deaths take place in low- and middle-income countries. Out of the 18 million premature deaths (under the age of 70) due to noncommunicable diseases in 2021, at least 38% were caused by CVDs. Most CVDs can be prevented by addressing behavioural and environmental risk factors such as tobacco use, unhealthy diet (including excess salt, sugar, and fats) and obesity, physical inactivity, harmful use of alcohol and air pollution [WHO Cardiovascular diseases 2025].

According to the Cardiovascular Disease Statistics published in 2022 by the European Society of Cardiology (ESC), ischaemic heart disease was the most common manifestation of incident CVD with

an estimated 5.8 million new cases in the 57 ESC member countries with data available. Its median age-standardised incidence rate was 293.3 per 100,000 inhabitants of each member country. There were 2.1 million new cases of stroke in the 57 ESC member countries with data available. The median age-standardised number of new cases per 100,000 inhabitants of each member country was 135.2 [Timmis et al. 2022]. Several investigations have highlighted possible interactions between anticonvulsant drugs and the cardiovascular system. Some of the older anticonvulsants (i.e. CBZ, phenobarbital, phenytoin, and primidone) have been associated with metabolic changes that may contribute to cardiovascular risk [Patorno et al. 2013, Mayer et al. 2024].

In a large cohort study with a median FU of 9 years, the hazard of incident CVD was higher in those receiving enzyme-inducing ASMs (EIASMs, including ESL) than in those without [Josephson et al. 2021]. The association was dose dependent and the absolute difference in hazard seems to reach clinical significance by approximately 10 years from first exposure. Due to this article a potential signal 'cardiovascular events' was raised, assessed as not validated and closed.

[Lee-Lane et al. 2021] found in another large cohort study that individuals with epilepsy prescribed ASMs are at an increased risk of major cardiovascular events (CVEs) compared with population controls. Being prescribed an enzyme-inducing ASM is reported as not associated with a greater risk of a major CVE compared to treatment with other ASMs. However, ESL was not included in this study.

In another large prospective cohort study in Canadian adults 45-85 years of age [Li et al. 2024], new onset CVEs, a composite of stroke, transient ischaemic attack (TIA), and myocardial infarction (MI) were more likely to occur in patients with epilepsy. 24.6% of this effect was mediated by strong EIASM use (CBZ, phenytoin, phenobarbital, primidone) and 4% by weak EIASM use (OXC, ESL, topiramate and rufinamide). Non-EIASM use contributed by 0.2%. If the components of the composite endpoint are considered, the proportion of strokes is 0.3%, TIAs 7.7%, and MI -2.8% for weak EIASM use. The proportion of strokes is -9.7%, of TIAs 8%, and of MI -2.8% for non-EIASM use. The cohort of epilepsy patients comprises 431 adults and the cohort of adults without epilepsy 26.797. The weak EIASM users were not stratified for the individual ASM.

[Nei et al. 2025] reviewed the potential of ASMs to increase the cardiovascular risk in epilepsy patients. The authors recommend to avoid sodium channel blockers in patients at risk for cardiac arrhythmias and to avoid EIASMs in patients with other cardiovascular risk factors, including atherosclerosis. However, they acknowledge that available data on ESL is scarce and that ESL is a weak inducer and may be an alternative to CBZ.

Of note, in a large retrospective study using United States (US) National Health and Nutrition Examination Survey, adult participants from 2013 to 2018 were included. Participants with epilepsy had increased 10-year atherosclerotic cardiovascular disease risk, despite similar or better awareness, treatment, and control of individual risk factors such as diabetes and hypertension. Results suggest that epilepsy is associated with numerous health behaviours leading to CVD, though the causal pathway is complex as these variables (income, depression, diet, exercise, smoking) generally served as confounders rather than mediators [Terman et al. 2021].

Clinical trial data

Incidence

The ISDB was searched by the SMQs 'ischaemic heart disease' and 'ischaemic central nervous system vascular conditions'. Incidences are given in percentages together with their 95% CIs for TEAEs and ADRs (=TEAEs assessed as at least possibly related by the investigator) in patients with epilepsy treated with ESL. Individual TEAEs/ADRs are given as MedDRA PTs.

Of note in DB clinical trials, TEAEs in the SOC 'cardiac disorders' show a higher incidence in ESL-treated elderly than in ESL-treated non-elderly patients.

a. Indication epilepsy / all studies
   - TEAEs: 3.9 (3.2; 4.6)
   - ADRs: 1.3 (0.9; 1.8)
   - Individual ADRs, incidence ≥0.1%:
     - 'angina pectoris': 0.1 (0.0; 0.3)
     - 'blood creatine phosphokinase increased': 1.0 (0.7; 1.4)

Seriousness

a. Indication epilepsy / all studies
   - Serious TEAEs: 16 patients (0.5%); 'angina pectoris' (3), 'arteriosclerosis coronary artery' (1), 'coronary artery disease' (1), 'myocardial infarction' (1), 'blood creatinine phosphokinase increased' (1), 'cerebral ischaemia' (1), 'cerebrovascular accident' (1), 'ischaemic stroke' (3), 'lacunar infarction' (1), 'transient ischaemic attack' (3)

TEAEs outcome (percentage of all patients exposed to ESL)

a. Indication epilepsy / all studies
   - recovered (3.1), recovered with sequelae (0.4), ongoing (0.7), died (0.1; 2 patients), unknown (0.2), recovering (<0.1)

Severity (percentage of all patients exposed to ESL, maximum severity in the individual patient)

a. Indication epilepsy / all studies
   - TEAEs: mild (2.1), moderate (0.8), severe (0.6)

<u>Post-marketing data</u>

Cumulatively up to 21 October 2025, the safety database was searched with the SMQs 'ischaemic heart disease' (broad and narrow) and 'ischaemic central nervous system vascular conditions'. Retrieved events comprise (PTs): 'angina pectoris' (1 serious, 1 non-serious solicited), 'coronary artery disease' (1 serious, 1 non-serious solicited), '(acute) myocardial infarction' (2 serious); 'cerebrovascular accident' (17, thereof 16 serious, 1 fatal), 'cerebral infarction' (1 serious), 'cerebral microembolism' (1 serious), 'transient ischaemic attack' (2 serious). Alternative explanations are available, confounding factors are present or co-suspect medication is reported for most of the cumulatively retrieved cases.

<u>Risk factors and risk groups:</u>

Risk factors for CAD include age, gender, diabetes, serum lipids, smoking, high blood pressure, and physical inactivity. Risk factors for cerebrovascular disease are essentially the same. Atrial fibrillation, heart failure and MI are other important risk factors for cerebrovascular disease.

<u>Preventability:</u>

By collecting further data on cardiovascular/cerebrovascular reactions, the MAH can better understand its true frequency in patients treated with ESL and provide better guidance to physicians and patients.

Impact on the risk-benefit balance of the product:

Impact is considered low. So far no particular risk suspected to be related to ESL has been identified.

Public health impact:

The potential impact in public health is considered low due to the low incidence of cardiovascular/cerebrovascular ischaemia in ESL-treated patients.

SVII.3.2. Presentation of the missing information

SVII.3.2.1 Missing information: exposure during pregnancy

Evidence source:

There have not been any prospective studies evaluating ESL in pregnant or lactating women. Women who were pregnant or lactating were not allowed to participate in ESL clinical studies. Women of childbearing potential were required to use an adequate and reliable method of contraception while participating in clinical studies. They were also required to perform a pregnancy test prior to participation and also at specific study visits.

If female patients of childbearing potential use hormonal contraceptives concomitantly with ESL without an alternative contraceptive method, e.g. barrier method, they are at risk of becoming pregnant because exposure to progestins, e.g. levels of levonorgestrel and ethinylestradiol, may be reduced, most probably by an induction of CYP3A4. As ESL adversely interacts with oral contraceptives, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped.

Overall, until 21 October 2025, 214 ESL exposure via parent cases were identified (mother-child cases counted as one case and child cases with ESL exposure during pregnancy without mother case counted as one case). Of these, 29 are clinical trial and 185 post-marketing cases. One case involving drug exposure during lactation was reported.

In each Periodic Safety Update Report (PSUR), data of all available case reports with confirmed ESL exposure on pregnancy outcomes according to the European Pregnancy Guideline EMEA/CHMP/313666/2005, are presented separately for prospective and retrospective cases.

To date (cumulative to 21 October 2025), the following ESL-exposed cases with congenital abnormalities are reported: polydactyly (lamotrigine as concomitant ASM); ectopic kidney, foetal growth restriction (, phenobarbital and topiramate as concomitant ASMs); hypospadias , lamotrigine and tiagabine as concomitant ASMs); talipes (lacosamide as concomitant ASM, overdose scheme); cytogenetic abnormality with spontaneous abortion CBZ as concomitant ASM); congenital knee dislocation , mechanical origin and not ESL appears the plausible for the dislocated knee); congenital anomaly, conjoined twins with spontaneous abortion levetiracetam as concomitant ASM); congenital anomaly (, lamotrigine as concomitant ASM); congenital anomaly (infant was exposed to ESL and levetiracetam); congenital skin dimple infant was exposed to ESL and levetiracetam all 3 trimester of pregnancy); congenital central nervous system anomaly exposure via father, foetus was diagnosed with exencephaly); neural tube defect ESL prior conception and during all pregnancy, concomitant medication not reported); congenital anomaly infant was exposed to ESL and lacosamide during all pregnancy); Trisomy 21 (, mother was medicated with ESL and lamotrigine); heart disease congenital (mother was medicated with ESL during all pregnancy, she switched from levetiracetam before pregnancy); neural tube defect , mother took ESL). All reported cases but one were patients on add-on treatment and the role of concomitant ASMs cannot be excluded.

Until 21 October 2025, 17 cases of spontaneous abortion have been reported (13 in post-marketing including 2 patients who experienced loss of pregnancy twice and 1 case of "abortion late", and 4 from clinical trials). At this point in time there is no evidence supporting a causal relationship between administration of ESL and spontaneous abortion.

Population in need of further characterisation:

All available drug exposure via parent cases from clinical trials and post-marketing experience to date are in line with the current knowledge of the product profile. Information on effects of ESL exposure during pregnancy on the foetus and the postnatal development is limited. From the available data no conclusions can be drawn. Most of the reported cases were patients on add-on treatment and the role of concomitant ASMs cannot be excluded. ESL should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. The MAH will continue to collect, evaluate and monitor information on ESL exposure via parent.

EURAP Registry

Since September 2011 pregnancy information related to ESL has been followed up within an observational Pregnancy Exposure Registry (Study BIA-2093-402), the EURAP. A Summary Report based on more than 14 years of monitoring pregnancies in women with epilepsy enrolled in the project, with particular focus on exposure to ESL is presented in Annex 7.1.

The report concluded that, although no specific adverse signals were observed, the numbers are too small to permit meaningful conclusions on the safety of ESL during pregnancy.

Monitoring of drug exposure via parent will continue to be performed by the MAH.

Clinical trial and PMS data

The following tables (Table SVII.1 and Table SVII.2) present cumulative data of all available case reports within the safety database with confirmed ESL exposure on pregnancy outcomes according to the European Pregnancy Guideline EMEA/CHMP/313666/2005, separately for prospective and retrospective cases. Prospective data of pregnancy exposure are acquired prior to the knowledge of the pregnancy outcome or prior to detection of a congenital malformation at prenatal examination (e.g. fetal ultrasound, serum markers). Retrospective data of pregnancy exposure are acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on prenatal testing. Table SVII.1 presents all pregnancy cases where the mother was exposed to ESL (monotherapy and polytherapy) while Table SVII.2 gives pregnancy cases where the mother was exposed to ESL as monotherapy only. All the cases presented are cumulative up to 21 Oct 2025.

Table SVII.1: All pregnancy cases where the mother was exposed to ESL as monotherapy and polytherapy (cumulative to 21 October 2025)

Pregnancy outcome **total cases per category (Prospective/ Retrospective)**	**Prospective cases Number**					**Retrospective cases Number**				
	Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)					**Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)**				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy: 0										
Spontaneous abortion: 17 (4P/ 13R)	4	3*				6	7*	1*	1*	3
Elective termination (foetal defects): 1 (0P/ 1R)							1	1*		
Elective termination (no foetal defects or unknown): 12 (6P/ 6R)	3	2*		1*	3	6	5*	1*	1*	
Stillbirth with foetal defect: 2 (0P/ 2R)							1			1
Stillbirth without fetal defects: 0										

Pregnancy outcome **total cases per category (Prospective/ Retrospective)**	**Prospective cases Number**					**Retrospective cases Number**				
	Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)					**Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)**				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Live birth with congenital anomaly: 10 (2P/ 8R)	1	2*	1*	1*		3	1	1*	5*	3
Live birth without congenital anomaly: 44 (25P/ 19R)	18	10*	1*	8*	4*	5	1*		12*	6
SUBTOTAL: 86 (37P/ 49R)	**26**	**17**	**2**	**10**	**7**	**20**	**16**	**4**	**19**	**13**
Live-birth (unknown health status): 34 (15P / 19R)		9	10*	9*		5	10*	8*	11*	4
Unknown or ongoing pregnancy: 103 (81P/ 21R)	19	17*	7*	11*	46	2	7*	7*	6*	10
TOTAL: 223 (133P/ 89R)	**45**	**43**	**19**	**30**	**53**	**26**	**33**	**19**	**36**	**27**

Pregnancy outcome **total cases per category (Prospective/ Retrospective)**	**Prospective cases** **Number**					**Retrospective cases** **Number**				
	Timing of exposure in pregnancy **(each applicable category, multiple categories per case possible)**					**Timing of exposure in pregnancy** **(each applicable category, multiple categories per case possible)**				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown

*multiple categories per case, P–prospective, R-retrospective

Source: Argus Safety™ database.

Table SVII.2: Pregnancy cases where the mother was exposed to ESL as monotherapy (data cumulative to 21 October 2025)

Pregnancy outcome **total cases per category (Prospective/ Retrospective)**	**Prospective cases** **Number**					**Retrospective cases** **Number**				
	Timing of exposure in pregnancy **(each applicable category, multiple categories per case possible)**					**Timing of exposure in pregnancy** **(each applicable category, multiple categories per case possible)**				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy: 0										
Spontaneous abortion: 5 (2P/ 3R)	2	2*				1	3*			
Elective termination (fetal defects): 0										

Pregnancy outcome **total cases per category (Prospective/ Retrospective)**	**Prospective cases** **Number** **Timing of exposure in pregnancy** **(each applicable category, multiple categories per case possible)**					**Retrospective cases** **Number** **Timing of exposure in pregnancy** **(each applicable category, multiple categories per case possible)**				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Elective termination (no foetal defects or unknown): 6 (3P/ 3R)	2	1*		1*	1	3	3*	1*		
Stillbirth with foetal defect: 1 (0P / 1R)										1
Stillbirth without fetal defects: 0										
Live birth with congenital anomaly: 1 (0P/ 1R)						1			1*	
Live birth without congenital anomaly: 12 (9P/ 3R)	9	6*		2*					3	
SUBTOTAL: 25 (14P/ 11R)	**13**	**9**	**0**	**3**	**1**	**5**	**6**	**1**	**4**	**1**
Live-birth (unknown health status): 8 (0P / 8R)						3	7*	4*	5*	
Unknown or ongoing pregnancy: 22 (16P/ 6R)	5	5*	1*	5*	7		1	1*	2*	3

Pregnancy outcome total cases per category (Prospective/ Retrospective)	Prospective cases Number Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)					Retrospective cases Number Timing of exposure in pregnancy (each applicable category, multiple categories per case possible)				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
TOTAL: 55 (30P / 25R)	**18**	**14**	**1**	**8**	**8**	**8**	**14**	**6**	**11**	**4**

*multiple categories per case, P–prospective, R-retrospective

Source: Argus Safety™ database.

ESL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The MAH will continue to collect, evaluate, and monitor information on ESL exposure via parent. Such information is defined as missing information in the current RMP.

SVII.3.2.2 Missing information: paediatric population (<2 years of age)

Evidence source:

ESL is approved in children aged above 6 years with POS with or without secondary generalisation as adjunctive therapy in the European Union (EU) and above 4 years in POS as adjunctive therapy and monotherapy in the US.

The safety and efficacy of ESL in children aged below 4 years has not yet been completely established and is still under clinical development.

Available data for children from clinical trials

The development of ESL in the paediatric population is detailed in the PIP (P/0197/2013; EMEA-000696-PIP02-M04).

To date, 5 trials in children have been completed: Studies BIA-2093-202, -208, -211, -212, and -305.

The Phase IIa study (BIA-2093-202) was conducted in children and adolescents with refractory POS.

In the DB Study BIA-2093-212, the preference of children with epilepsy for ESL suspension formulations with different flavors was compared.

Study BIA-2093-305 is a DB, placebo-controlled Phase III study in 304 children aged from 2 to 18 years, with POSs refractory to treatment with 1 or 2 other ASMs to evaluate the efficacy and safety of ESL. Depending on tolerance, patients could be treated with ESL doses of 10, 20, or 30 mg/kg body weight QD (maximum daily dose 1200 mg) during the 12-week maintenance period.

Study BIA-2093-208 is a DB, placebo-controlled Phase II study to evaluate the effects of ESL in comparison with placebo as adjunctive therapy on cognition in 123 children aged 6 to 16 years with partial-onset seizures refractory to treatment with one or two other ASMs. Depending on tolerance, patients could be treated with ESL doses of 10, 20, or 30 mg/kg body weight QD (maximum daily dose 1200 mg) during the 8-week maintenance period. Most of the patients (69 of 83 [83.1%]) received 30 mg/kg ESL QD or matching placebo (37 of 40 [92.5%]).

Study BIA-2093-211 is an OL 2-dose level trial to evaluate ESL (oral solution 50 mg/ml, QD) PK, safety and tolerability as adjunctive therapy in infants (aged from 1 month to <2 years) with refractory epilepsy with POS. After completion of Study BIA-2093-211, parent(s) or guardian(s) could choose to allow their child to continue treatment with ESL for 1 year in Study BIA-2093-211/EXT. During this 1-year study, subjects were grouped by treatment.

After completion of Part I of Studies 305 and 208, patients could enter a 1-year OL extension period (Part II) during which all patients were treated with ESL doses of 10 to 30 mg/kg body weight QD (maximum daily dose 1200 mg).

In placebo-controlled studies involving patients aged from 2 to 18 years with POS (238 patients treated with ESL and 189 with placebo), 35.7% of patients treated with ESL and 19% of patients treated with placebo experienced adverse reactions. The most common adverse reaction in the group treated with ESL were diplopia (5.0%), somnolence (8.0%) and vomiting (4.6%).

The adverse reaction profile of ESL is generally similar across age groups. In the age group from 6 to 11 years of age, the most common adverse reactions observed in more than two patients treated with ESL were diplopia (9.5%), somnolence (7.4%), dizziness (6.3%), convulsion (6.3%) and nausea (3.2%); in the age group from 12 to 18 years were somnolence (7.4%), vomiting (4.2%), diplopia (3.2%) and fatigue (3.2%). The safety of Zebinix in children aged 6 years and below has not yet been established. In patients 1 month to <2 years of age, with refractory epilepsy with partial-onset seizures there were no new safety signals observed, and the safety profile was the same as for other paediatric groups.

The safety profile of ESL was generally similar between adult and paediatric patients, except for agitation (common, 1.3%) and abdominal pain (common, 2.1%) which were more common in children than in adults. Dizziness; somnolence; vertigo; asthenia; gait disturbance; tremor; ataxia; balance disorder; vision blurred; diarrhoea; rash and hyponatraemia were less common in children than in adults. Dermatitis allergic (uncommon, 0.8%) was reported only in the paediatric population.

Long-term safety data in the paediatric population obtained from OL extensions of the Phase III study was consistent with the known safety profile of the product with no new findings of concern.

TEAEs of Studies BIA-2093-202, 211 and 305 were pooled and analysed by age groups. Only in OL parts, patients below 2 years of age were included: 12 male (10.7 person-years) and 11 female (10.9 person-years), for exposure see Table SIII.5. Results of the pooled analysis are provided in for TEAEs in Table SVII.3 and for at least possibly related TEAEs in Table SVII.4.

Table SVII.3: Overview of TEAEs by age group in children with epilepsy – open-label part of studies BIA-2093-202, 208 and 305; only TEAEs that occurred in patients <2 years

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Total number of patients	23 (100)	77 (100)	147 (100)	148 (100)
Total number of patients with TEAE	19 (82.6)	59 (76.6)	103 (70.1)	96 (64.9)
Blood and lymphatic disorders	3 (13.0)	6 (7.8)	6 (4.1)	7 (4.7)
Anaemia	1 (4.3)	3 (3.9)	1 (0.7)	1 (0.7)
Hypochromic anaemia	2 (8.7)	0	0	0
Cardiac disorders	1 (4.3)	2 (2.6)	3 (2.0)	3 (2.0)
Atrioventricular block first degree	1 (4.3)	0	0	0
Eye disorders	2 (8.7)	1 (1.3)	10 (6.8)	14 (9.5)

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Conjunctivitis	1 (4.3)	0	0	0
Strabismus	1 (4.3)	0	0	0
Gastrointestinal disorders	6 (26.1)	22 (28.6)	28 (19.0)	20 (13.5)
Constipation	1 (4.3)	1 (1.3)	1 (0.7)	1 (0.7)
Enterocolitis	1 (4.3)	2 (2.6)	1 (0.7)	2 (1.4)
Flatulence	2 (8.7)	1 (1.3)	0	0
Teething	2 (8.7)	0	0	0
Vomiting	2 (8.7)	9 (11.7)	17 (11.6)	9 (6.1)
General disorders and administration site conditions	1 (4.3)	18 (23.4)	18 (12.2)	22 (14.9)
Pyrexia	1 (4.3)	15 (19.5)	9 (6.1)	13 (8.8)
Immune system disorders	1 (4.3)	0	3 (2.0)	2 (1.4)
Allergy to arthropod bite	1 (4.3)	0	0	0
Infections and infestations	15 (65.2)	48 (62.3)	69 (46.9)	53 (35.8)
Acute tonsillitis	1 (4.3)	2 (2.6)	4 (2.7)	4 (2.7)
Bronchitis	5 (21.7)	12 (15.6)	7 (4.8)	5 (3.4)
Exanthema subitum	1 (4.3)	0	0	0
Gastrointestinal infection	1 (4.3)	0	0	0
Laryngitis	1 (4.3)	1 (1.3)	1 (0.7)	1 (0.7)
Nasopharyngitis	3 (13.0)	13 (16.9)	16 (10.9)	14 (9.5)
Otitis media	1 (4.3)	0	2 (1.4)	2 (1.4)
Pharyngitis	3 (13.0)	7 (9.1)	7 (4.8)	7 (4.7)
Respiratory tract infection	4 (17.4)	11 (14.3)	8 (5.4)	7 (4.7)
Respiratory tract infection viral	3 (13.0)	3 (3.9)	6 (4.1)	5 (3.4)
Rhinitis	1 (4.3)	8 (10.4)	7 (4.8)	5 (3.4)
Upper respiratory tract infection	1 (4.3)	14 (18.2)	4 (2.7)	1 (0.7)
Urinary tract infection	1 (4.3)	4 (5.2)	1 (0.7)	1 (0.7)
Viral infection	2 (8.7)	9 (11.7)	7 (4.8)	4 (2.7)

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Viral rash	1 (4.3)	1 (1.3)	0	0
Wound infection	1 (4.3)	0	0	0
Injury, poisoning and procedural complications	2 (8.7)	5 (6.5)	11 (7.5)	15 (10.1)
Exposure to toxic agent	1 (4.3)	0	0	0
Overdose	1 (4.3)	0	0	0
Investigations	7 (30.4)	26 (33.8)	10 (6.8)	24 (16.2)
Alanine aminotransferase increased	2 (8.7)	1 (1.3)	0	1 (0.7)
Blood creatinine increased	1 (4.3)	0	0	0
Blood glucose increased	1 (4.3)	0	0	0
Body temperature increased	2 (8.7)	0	0	3 (2.0)
Electrocardiogram PR prolongation	1 (4.3)	0	0	0
Hepatic enzyme increased	1 (4.3)	1 (1.3)	1 (0.7)	1 (0.7)
Metabolism and nutrition disorders	1 (4.3)	6 (7.8)	6 (4.1)	1 (0.7)
Hyponatraemia	1 (4.3)	0	1 (0.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.3)	2 (2.6)	1 (0.7)	0
Astrocytoma, low grade	1 (4.3)	0	0	0
Nervous system disorders	7 (30.4)	28 (36.4)	42 (28.6)	48 (32.4)
Akathisia	1 (4.3)	0	0	0
Circadian rhythm sleep disorder	1 (4.3)	2 (2.6)	0	0
Convulsion	2 (8.7)	19 (24.7)	23 (15.6)	16 (10.8)
Epilepsy	1 (4.3)	1 (1.3)	2 (1.4)	1 (0.7)
Febrile convulsion	1 (4.3)	1 (1.3)	0	0
Infantile spasms	1 (4.3)	0	0	0

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Mental retardation	1 (4.3)	0	0	0
Somnolence	3 (13.0)	6 (7.8)	11 (7.5)	9 (6.1)
Tremor	1 (4.3)	0	0	3 (2.0)
Respiratory, thoracic and mediastinal disorders	3 (13.0)	9 (11.7)	11 (7.5)	12 (8.1)
Adenoidal hypertrophy	1 (4.3)	1 (1.3)	0	0
Respiratory disorder	1 (4.3)	0	3 (2.0)	0
Rhinorrhoea	1 (4.3)	0	1 (0.7)	0
Vasomotor rhinitis	1 (4.3)	0	1 (0.7)	0
Skin and subcutaneous tissue disorders	2 (8.7)	8 (10.4)	10 (6.8)	7 (4.7)
Dermatitis allergic	1 (4.3)	2 (2.6)	3 (2.0)	0
Dermatitis atopic	1 (4.3)	1 (1.3)	0	0
Dermatitis diaper	1 (4.3)	0	0	0
Surgical and medical procedures	1 (4.3)	1 (1.3)	3 (2.0)	3 (2.0)
Cleft palate repair	1 (4.3)	0	0	0
Ear tube insertion	1 (4.3)	0	0	0

PT-preferred term, SOC-system organ class, TEAE-treatment-emergent adverse event.
Source: ISDB

Table SVII.4: Overview of at least possibly related TEAEs by age group in children with epilepsy – open-label part of studies BIA-2093-202, 208 and 305, only PTs included that occurred in the <2 years group

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Total number of patients	23 (100)	77 (100)	147 (100)	148 (100)
Total number of patients with at least possibly related TEAEs	6 (26.1)	31 (40.3)	40 (27.2)	30 (20.3)
Cardiac disorders	1 (4.3)	1 (1.3)	1 (0.7)	0
Atrioventricular block first degree	1 (4.3)	0	0	0

SOC PT	<2 years n (%)	2-5 years n (%)	6-11 years n (%)	12-18 years n (%)
Injury, poisoning and procedural complications	1 (4.3)	0	0	2 (1.4)
Overdose*	1 (4.3)	0	0	0
Investigations	2 (8.7)	11 (14.3)	4 (2.7)	8 (5.4)
Alanine aminotransferase increased	1 (4.3)	0	0	0
Electrocardiogram PR prolongation	1 (4.3)	0	0	0
Metabolism and nutrition disorders	1 (4.3)	2 (2.6)	2 (1.4)	0
Hyponatraemia	1 (4.3)	0	0	0
Nervous system disorders	3 (13.0)	13 (16.9)	18 (12.2)	18 (12.2)
Convulsion	1 (4.3)	6 (7.8)	7 (4.8)	4 (2.7)
Somnolence	3 (13.0)	5 (6.5)	10 (6.8)	7 (4.7)
Tremor	1 (4.3)	0	0	2 (1.4)
Skin and subcutaneous tissue disorders	1 (4.3)	1 (1.3)	1 (0.7)	1 (0.7)
Dermatitis allergic	1 (4.3)	0	1 (0.7)	0

PT-preferred term, QD-once daily, SOC-system organ class, TEAE-treatment-emergent adverse event.

* This event refers to a [redacted]-year old patient who was on ESL 25mg/kg QD (Protocol maximum dose of 20mg/kg). No adverse event associated. After dose reduction to protocol values, seizures occurred.

Source: ISDB

The status of clinical trial data pertaining to the different age groups, for PK in particular, in children is as follows:

- Pre-term newborns: no clinical trial data available
- Neonate (birth to 27 days): no clinical trial data available
- Infants and toddlers (28 days to 23 months):
    - BIA-2093-211: high inter-individual variability was found in the PK of eslicarbazepine in both age groups (≥1 to <6 months) and (≥6 to <24 months) at the dose levels

tested. Values for time to reach maximum concentration and half-life were similar in both age cohorts. At a dose of 20 mg/kg, the geometric mean ratio (90% CI) was 2.12 (1.33; 3.37) for C_{max} and 2.25 (1.30; 3.91) for AUC in the dosing interval, indicating higher exposure to eslicarbazepine in the age cohort (≥6 to <24 months).

- Children (2 years to e.g. 11 years) and adolescents (e.g. 12 years to 17 years):
  - BIA-2093-202: ESL PK was investigated in children and adolescents from 2 to 17 years. Eslicarbazepine C_{max} and AUC were dose-proportional (5 mg / 15 mg / 30 mg/kg/day QD). Age did not affect eslicarbazepine C_{max} but AUC depended on age, due to a faster plasma clearance of eslicarbazepine in younger versus older children;

Available data for children from post-marketing sources

Most commonly reported PTs are (frequency ≥ 10): 'seizure' (73 serious); '*off label use' (64 non-serious)*; 'drug ineffective' (36, thereof 2 serious); '*product use issue' (35 non-serious)*; 'dizziness' (21, thereof 1 serious); 'rash' (20, thereof 3 serious); 'overdose' (20 non-serious); '*inappropriate schedule of product administration' (19 non-serious)*; 'hyponatraemia' (18, thereof 13 serious); 'underdose' (16 non-serious); 'epilepsy' (15, thereof 14 serious); 'somnolence' (14, thereof 3 serious); 'irritability' (12 non-serious); '*drug dose titration not performed' (12 non-serious)*; 'headache' (10 non-serious).

The clinical development of ESL in children is ongoing according to PIP (P/0197/2013; EMEA-000696-PIP02-M04).

Anticipated risk/consequence of the missing information:

Considering available data, the safety profile in paediatric patients is comparable to adult patients in epilepsy.

SVII.3.2.3 Missing information: elderly population

Evidence source:

Data for elderly patients from clinical trials

Table SVII.5: Adult epilepsy ESL-treated patients in completed clinical trials by MedDRA PT, non-elderly vs. elderly, with at least 3% difference in incidence of TEAEs between groups

	18 – 64 years		≥65 years	
	TEAEs n (%)	**At least possibly related TEAEs**	**TEAEs n (%)**	**At least possibly related TEAEs**
Total number of patients	2562 (100)	2562 (100)	143 (100)	143 (100)
Total number of patients with TEAE	2052 (80.1)	1500 (58.5)	110 (76.9)	80 (55.9)
Cataract	3 (0.1)	0	5 (3.5)	2 (1.4)
Diplopia	187 (7.3)	172 (6.7)	6 (4.2)	6 (4.2)

	18 – 64 years		≥65 years	
	TEAEs n (%)	**At least possibly related TEAEs**	**TEAEs n (%)**	**At least possibly related TEAEs**
Vomiting	196 (7.7)	124 (4.8)	5 (3.5)	3 (2.1)
Gait disturbance	39 (1.5)	31 (1.2)	8 (5.6)	6 (4.2)
Gamma-glutamyltransferase increased	27 (1.1)	16 (0.6)	6 (4.2)	5 (3.5)
Hyponatraemia	73 (2.8)	65 (2.5)	15 (10.5)	13 (9.1)
Back pain	137 (5.3)	16 (0.6)	12 (8.4)	1 (0.7)
Convulsion	48 (1.9)	17 (0.7)	8 (5.6)	3 (2.1)
Dizziness	665 (26.0)	542 (21.2)	23 (16.1)	20 (14.0)
Headache	546 (21.3)	248 (9.7)	18 (12.6)	11 (7.7)
Somnolence	367 (14.3)	324 (12.6)	15 (10.5)	13 (9.1)
Hypertension	80 (3.1)	16 (0.6)	14 (9.8)	5 (3.5)

ESL-eslicarbazepine acetate, MedDRA-Medical Dictionary for Regulatory Activities, PT-preferred term, SOC-system organ class, TEAE-treatment-emergent adverse event.
Source: ISDB

In completed clinical trials in the indication epilepsy, 143 elderly (≥65 years) patients were exposed to ESL. In completed clinical trials in the indication neuropathic pain (unapproved indication), 674 elderly patients were exposed to ESL and 156 patients were exposed to placebo. The overall incidences of TEAEs and at least possibly related TEAEs are comparable between elderly and non-elderly patients in the indication epilepsy. In the indication neuropathic pain, the overall incidence of TEAEs and at least possibly related TEAEs was approximately 10% higher in elderly than in non-elderly adult patients, which may be related to higher comorbidities. Elderly patients reported vertigo, nausea/vomiting, dizziness and hyponatraemia more frequently; however, with the same frequency category (common).

Data for elderly patients from PMS sources

Most commonly reported suspected ADRs from PMS sources (including serious solicited events) included 'seizure' (896), 'hyponatraemia'/'blood sodium decreased' (624), 'dizziness' (285), 'rash' (198), and 'somnolence' (168).

From PMS, data of 2071 events referring to elderly patients are available. Most commonly reported events referring to elderly (including serious and non-serious solicited events) are: 'hyponatraemia'/'blood sodium decreased' (207), 'seizure' (87), 'dizziness' (75), 'somnolence' (42), 'rash', and 'nausea' (36 each).

The events reported from post-marketing sources are well in line with the known ESL safety profile in elderly patients, with hyponatraemia being a commonly reported ADR in this age group.

Concerning hyponatraemia, the warning in the current product information is considered appropriate to alert elderly patients and their physicians.

Anticipated risk/consequence of the missing information:

Available clinical trial data from elderly patients in the indication epilepsy and neuropathic pain (unapproved indication) indicate that the pattern and nature of events were similar with those of younger age groups except for hyponatraemia that was more frequent. The events reported from post-marketing sources are well in line with the known ESL safety profile in elderly patients, with hyponatraemia being a commonly reported ADR in this age group. Concerning hyponatraemia, the warning in the current SmPC is considered appropriate to alert elderly patients and their physicians.

SVII.3.2.4 Missing information: Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

Evidence source:

Long-term safety information was gathered from OL extension of studies: BIA-2093-305 (Part II – V) and BIA-2093-208 (Part II & III), including a total of 211 children exposed to a period of up to 72 months to ESL. From the gathered information no safety concerns regarding possible long-term effects on development, either cognitive, physical or physiological were found.

Furthermore, study 208 evaluated specifically the effects of ESL on cognitive function in children with POS.

Neurocognitive evaluation results:

The primary objective of this study was to evaluate the effects of ESL on cognition, in comparison with placebo, as adjunctive therapy in children aged 6 to 16 years-old with refractory partial-onset seizures over a 12-week DB period. The Cognitive Drug Research (CDR) System was selected to assess these changes in cognitive function as the system has been previously used and validated in clinical studies in both adult and paediatric epileptic patients (age 12 to 17 years) receiving different ASMs [Edgar and Wesnes. 2008; Wesnes et al. 2009; Wesnes and Busner. 2013]. The primary endpoint was the change from baseline to the end of the DB period in the per-protocol (PP) population for the composite Power of Attention measure; a measure which reflects focused attention and the speed of information processing.

The outcome of the analyses on the PP population was that at the end of the DB period there were no significant differences between ESL and placebo, either when analysed as a single group or divided in the 2 age cohorts (all P>0.48). However, a non-inferiority analysis failed to reject the null hypothesis that the change from Baseline in the Power of Attention score in the ESL group was at least 121 msec inferior to the placebo group for all age groups.

In the superiority testing for the Power of Attention, there was no significant difference between ESL and placebo for the overall age group or among the two age groups, in a study adequately powered study to detect such an effect. In fact there was a non-significant benefit of ESL over placebo with an effect size of 0.28. Further, in the OL extension, maturational development on this domain of cognition at least matched, if not exceeded, the expected rate of development seen in an age-matched cohort from the CDR System database.

The patients entered a one-year OL FU after the end of the DB period. Over the year, the patients showed a mean improvement in Power of Attention of 182 msec (235 msec for the 6 to 11 year old patients and 144 for the 12 to 16 year old patients). Figure 1 shows cross-sectional year by year changes in Power of Attention in a large sample of healthy individuals aged 6 to 17 years. From 6 to 16 years of age the average yearly maturational improvement in healthy children was 70 msec. Thus in the present study, the maturational development during the one-year OL FU clearly showed no evidence of falling behind what would be expected for healthy children (Figure 1).

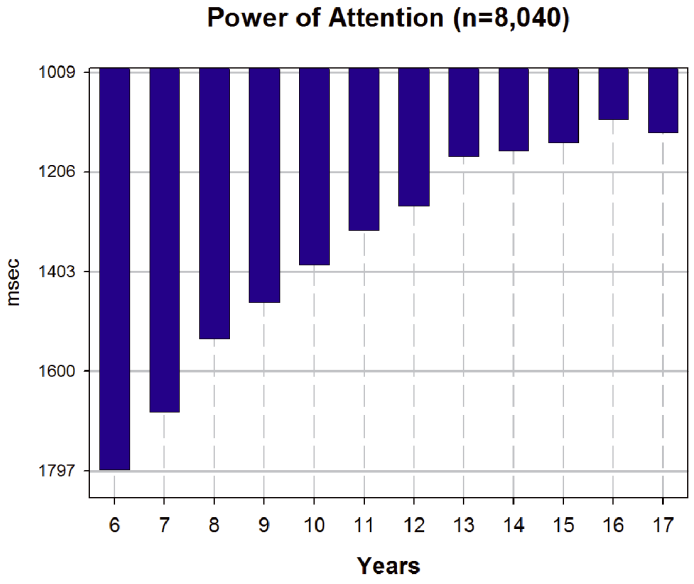

Figure 1 – CSR BIA-2093-208 (Parts I and II)

This study has therefore identified no evidence that ESL impairs focused attention and information processing. Furthermore, when subsequently administered for a year, there was no evidence of any reduction in the expected rate of development of this important aspect of cognitive function.

Secondary and supportive endpoints:

Of the four secondary cognitive domains assessed in this study, ESL was found not to negatively influence sustained attention, working memory or memory retrieval speed.

ESL did have a statistically reliable negative effect on the Episodic Memory Index, a measure of delayed recognition of previously presented information. However, the two groups had notably different pre-study scores on this measure, the ESL group being initially superior to placebo, and the effect may instead have represented 'regression to the mean'. Importantly, during the one-year FU, the group previously treated with ESL caught up with the group who initially received placebo; indicating that there was no long-term consequence for the possible effects seen in the DB period.

In conclusion, the findings of this study are that in epilepsy patients aged 6 to 16 years, ESL does not thus appear to have negative consequences for attention, information processing and working memory in, or in the longer term for episodic memory.

Anticipated risk/consequence of the missing information:

The clinical data gathered on long-term use of ESL in the paediatric population as well as from preclinical data available to date presents evidence that no deleterious effects on either cognitive, physical or physiological development are known. Nevertheless the MAH will continue to monitor long-term effects on brain development, learning, intelligence, growth, endocrine function, and puberty as missing information through routine pharmacovigilance. Regarding children of childbearing potential, all pregnancies are presently under close monitoring as missing information. This includes providing information from ESL-exposed pregnancies. This evaluation is not restricted to the adult population, and therefore any new pregnancy information in patients below 18 years old will be followed up similarly.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cutaneous adverse reactions
Important potential risks	• Cardiovascular/cerebrovascular ischaemia •
Missing information	• Exposure during pregnancy • Paediatric population (<2 years of age) • Elderly population • Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction FU questionnaires for cutaneous adverse reactions and cardiovascular / cerebrovascular ischaemia:

To fully document and assess all safety reports of serious suspected adverse cardiovascular / cerebrovascular reaction and serious suspected adverse cutaneous reaction, specific FU questionnaires are sent to the reporters (Annex 4). The return of questionnaires is systematically checked and the content of returned questionnaires is reported in Council for International Organizations of Medical Sciences (CIOMS).

Other forms of routine pharmacovigilance activities for safety concerns:

EURAP Registry

Since September 2011 pregnancy information related to ESL has been followed up within an observational Pregnancy Exposure Registry (Study BIA-2093-402), the EURAP, with the aim of better characterizing missing information regarding ESL Exposure during pregnancy .

Monitoring of drug exposure via parent will continue to be performed by the MAH and relevant data from this registry will continue to be monitored within the ESL Periodic Safety Update Report (PSUR).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are currently no required additional pharmacovigilance activities to address specific safety concerns.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are currently no ongoing or planned additional pharmacovigilance activities. No further studies have been planned since the last update to the pharmacovigilance plan.

The previous Category 3 pharmacovigilance activity, Study BIA-2093-402 (EURAP Registry), has been completed and a summary report is provided in Annex 7.1. More details are provided in Section SVII.3.2.1.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no post-authorisation efficacy studies which are a specific obligation of the MAH.

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

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Cutaneous adverse reactions	Routine risk communication: SmPC section 4.3, 4.4 and 4.8, and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Routine activities are sufficient. Recommendation for discontinue ESL, if signs or symptoms of hypersensitivity, or SCARs (SJS/TEN, DRESS) is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Cardiovascular/cerebrovascular ischaemia	Routine risk communication: none. Routine risk minimisation activities recommending specific clinical measures to address the risk: none. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Pregnancy	Routine risk communication: SmPC section 4.6, and in PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Routine activities are sufficient. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Paediatric population (<2 years of age)	Routine risk communication: SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2, and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Routine activities are sufficient. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Elderly population	Routine risk communication: SmPC section 4.2, 5.1 and 5.2, and PL section 3.

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Routine activities are sufficient. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Long terms effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	Routine risk communication: none. Routine risk minimisation activities recommending specific clinical measures to address the risk: none. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription

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 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cutaneous adverse reactions	Routine risk communication: SmPC section 4.3, 4.4 and 4.8, and PL section 4. Additional risk minimisation measures: none.	FU questionnaire.
Cardiovascular/cerebrovascular ischaemia	No risk minimisation measures.	FU questionnaire.
Pregnancy	Routine risk communication: SmPC section 4.6, and PL section 2. Additional risk minimisation measures: none.	EURAP Registry.
Paediatric population (<2 years of age)	Routine risk communication: SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2, and PL section 2. Additional risk minimisation measures: none.	None.
Elderly population	Routine risk communication: SmPC section 4.2, 5.1 and 5.2, and PL section 3.	None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: none.	
Long terms effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	No risk minimisation measures.	None.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zebinix® (eslicarbazepine acetate)

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

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

This summary of the RMP for Zebinix® should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 Zebinix®'s RMP.

I. The medicine and what it is used for

Zebinix® is authorised as monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy and as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation. It contains eslicarbazepine acetate (ESL) as the active substance, and it is given as an oral tablet or oral suspension.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zebinix®, together with measures to minimise such risks and the proposed studies for learning more about Zebinix®'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 medicine's legal status — the way a medicine is supplied to the patient (e.g. 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 Zebinix® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Zebinix® 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 Zebinix®. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Cutaneous adverse reactions
Important potential risks	• Cardiovascular/cerebrovascular ischaemia
Missing information	• Exposure during pregnancy • Paediatric population (< 2 years of age) • Elderly population •Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

II.B Summary of important risks

Important identified risk: Cutaneous Adverse Reactions

Evidence for linking the risk to the medicine	Skin rash may affect 1 to 10 ESL users in 100. Hypersensitivity (allergic reactions) may affect 1 to 10 ESL users in 1000. Very rare but serious skin side effects that involve mucous membranes, large areas of the skin, blisters, bloodshot skin may occur with treatment of the chemically related ASMs carbamazepine (CBZ) and oxcarbazepine (OXC) and it cannot be excluded to also occur with Zebinix®. Patients with certain gene variants are more likely to develop serious skin side effects to CBZ than those without these gene variants.
Risk factors and risk groups	More than 200 medications, among them CBZ and other anti convulsants, have been associated with the occurrence of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Risk

	is usually restricted to the first weeks of drug intake. Other conditions causing SJS or TEN are infections and malignancies. Several risk factors for drug-hypersensitivity have been identified: drug related aspects (hapten/pro-hapten reaction concept), type of treatment regimen (intermittent>repeated>continuous), host-related: gender (female>male), and ethnicity. HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing severe cutaneous adverse reactions (SCAR) known as SJS when treated with CBZ. The chemical structure of ESL is similar to that of CBZ, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS after treatment with ESL. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these patients should be screened for this allele before starting treatment with CBZ or chemically-related compounds. If patients of these origins are tested positive for HLA-B*1502 allele, the use of ESL may be considered if the benefits are thought to exceed risks. Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered. The prevalence of the HLA-B*1502 allele is negligible in sampled individuals of European descent, African, Hispanic, and in Japanese and Koreans (<1%). There is some data that suggest HLA-A*3101 is associated with an increased risk of CBZ-induced cutaneous ADRs including SJS, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), or less severe acute generalised exanthematous pustulosis and maculopapular rash in people of European descent and the Japanese. The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 5% in European populations and about 10% in Japanese population. The presence of HLA-A*3101 allele may increase the risk for CBZ-induced cutaneous reactions (mostly less severe) from 5.0% in the general population to 26.0% among patients of European ancestry, whereas its absence may reduce the risk from 5.0 3.8%. There are insufficient data supporting a recommendation for HLA-A*3101

	screening before starting CBZ or chemically-related compounds treatment. If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of CBZ or chemically-related compounds may be considered if the benefits are thought to exceed the risks.
Risk minimisation measures	Routine risk minimisation measures: Routine risk communication - SmPC section 4.3, 4.4 and 4.8, and PL section 4. Additional risk minimisation measures: None.

Important potential risk: Cardiovascular/cerebrovascular ischaemia

Evidence for linking the risk to the medicine	Some of the older anticonvulsants (i.e. CBZ, phenobarbital, phenytoin, and primidone) have been associated with metabolic changes that may contribute to cardiovascular risk. At present, available data do not indicate that there is an increased cardiovascular or cerebrovascular risk in ESL users.
Risk factors and risk groups	Risk factors for coronary artery disease include age, gender, diabetes, serum lipids, smoking, high blood pressure, and physical inactivity. Risk factors for cerebrovascular disease are essentially the same. Atrial fibrillation, heart failure and myocardial infarction are other important risk factors for cerebrovascular disease.
Risk minimisation measures	No risk minimisation measures

Missing information: Exposure during Pregnancy

Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: SmPC section 4.6, and PL section 2. Additional risk minimisation measures: None.

Missing information: Paediatric population (<2 years of age)

Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2, and PL section 2 Additional risk minimisation measures:

	None.

Missing information: Elderly population

Risk minimisation measures	Routine risk minimisation measures: Routine risk communication: SmPC section 4.2, 5.1 and 5.2, and PL section 3. Additional risk minimisation measures: None.

Missing information: Long terms effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

Risk minimisation measures	No risk minimisation measures

II.C Post-authorisation 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 obligation of Zebinix®.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

PART VII: ANNEXES

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Annex 4 - Specific adverse drug reaction follow-up forms

The following are provided overleaf:

- Detailed Instructions for follow-up of Safety Reports through a specific questionnaire
- Serious adverse Cardiovascular/Cerebrovascular Reaction report form
- Serious Adverse Cutaneous Reaction report form

Annex 4.1 Detailed instructions for follow-up of safety reports through a specific questionnaire

DETAILED INSTRUCTIONS FOR FOLLOW-UP OF SAFETY REPORTS THROUGH A SPECIFIC QUESTIONNAIRE

This instruction document aims at ensuring that the relevant pharmacovigilance representative will perform the appropriate actions to facilitate collection of data, namely:

For all safety reports received regarding:

a. A serious Adverse Cardiovascular/Cerebrovascular reaction or
b. A serious Adverse Cutaneous Reaction

The following actions should be performed:

- A specific questionnaire form shall be sent to the reporter for follow-up (Questionnaires attached).
- Follow up contacts should be conducted in order to obtain all information required to fully document and assess the report.
- All follow-up attempts shall be documented;
- Two reminders and a closing letter should be sent to the reporter within 3 months after initial receipt of the report.
- If a case of a Severe cutaneous reaction such as Stevens Johnson Syndrome or Toxic Epidermal Necrolysis is received, ask the reporter if results of genotyping (HLA-A*3101 or HLA-B*1502) are available or pending. Do not ask the reporter to prescribe the tests. The relevance of the tests for individual cases should be evaluated by the reporter.

For any matters related to these instructions or clarification of its content, please contact:

Annex 4.2 Serious adverse cardiovascular/cerebrovascular reaction report form

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

1. IDENTIFICATION Nº/ COUNTRY	**2.** DRUG: **4.** CLINICAL TRIAL ☐ No ☐ Yes Protocol nº: Centre nº: Patient nº	**3.** DATE OF THIS REPORT: (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

A. GENERAL INFORMATION

TYPE OF REPORT: ☐ Initial ☐ Follow-Up # _____

5. **RAPPORTEUR**

Name: _____

Address: _____

_____

_____

Phone number: _____

Email: _____

B. PATIENT INFORMATION

6. PATIENT INITIALS (first,last)	7. **DATE OF BIRTH** (dd/mmm/yyyy):	8. **AGE**:	9. **SEX**:	**10. ETHNIC GROUP:**	**11.**
_____	__ __ / __ __ / __ __ 12. **OCCUPATION** _____	_____	☐ Male ☐ Female	☐ Caucasian ☐ African (Black) ☐ Asian ☐ Other, specify _____	**HEIGHT** _____ (cm) **WEIGHT** _____(kg)

C. ADVERSE REACTION INFORMATION

13. **ADR TERM** (Signs/symptoms if no diagnosis made)	14. **ONSET DATE** (dd/mmm/yyyy):	15. **OFFSET DATE** (dd/mmm/yyyy) OR ☐ ongoing
	__ __ / __ __ __ / __ __ __ __	__ __ / __ __ __ / __ __ __

16. **DESCRIPTION**: (include relevant tests; include dates, continue on last page or add additional page(s) if necessary):

_____

_____

_____

_____

_____

CHECK IF ATTACHED: ☐ Discharge report ☐ Autopsy report ☐ ECG ☐ Laboratory or other test results

17. Seriousness

☐ **Non-serious**

☐ **Serious. Why? (Check one or more):**

- ☐ **fatal**
- ☐ **life-threatening**
- ☐ **persistent or significant disability/incapacity**
- ☐ **congenital anomaly/birth defect**
- ☐ **required/prolonged hospitalization Admission date __ __ / __ __ __ / __ __ __ __ Discharge date __ __ / __ / __ __ __ _**
- ☐ **other medically important condition**

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

TYPE OF EVENT

I. ELECTROCARDIOGRAPHIC ABNORMALITIES

ECG DONE? ☐ Yes ☐ No If yes, please complete:

Rates and intervals

Ventricular Rate per minute: _____
P-R Interval (hundredths of a second):_____
or ☐ fully paced ☐ Atrial Fib ☐ Unknown
QRS interval (hundredths of a second):_____
or ☐ fully paced ☐ Unknown
Q-T interval (hundredths of a second):_____
Or ☐ fully paced ☐ Unknown

Rhythm

☐ Normal Sinus (including S. tach, S. brady, S. arrhy, 1 degree AV block)
☐ 2nd degree AV block, Mobitz I (Wenckebach)
☐ 2nd degree AV block, Mobitz II ☐ 3rd degree AV block/AV dissociation
☐ Atrial fibrillation/atrial flutter ☐ Nodal ☐ Paced
☐ Other or combination of above (list):_____

Ventricular conduction abnormalities

IV BLOCK ☐ Yes ☐ No ☐ fully paced ☐ Unknown
Pattern: ☐ left ☐ right ☐ indetermined
☐ Complete (QRS interval= 0.12 sec or greater)
☐ Incomplete (QRS interval= 0.10 0r 0.11 sec)
☐ Unknown
Hemiblock:
☐ No ☐ left ant ☐ left post ☐ fully paced ☐ unknown

Arrhythmias

ATRIAL PREMATURE BEATS ☐ No ☐ Unknown
☐ Atr ☐ Atr Aber
VENTRICULAR PREMATURE BEATS ☐ No ☐ Unknown ☐ Simple ☐ Multifoc ☐ Pairs ☐ Run ☐ R on T

Myocardial infarction

☐ Yes ☐ No ☐ unknown
☐ Anterior ☐ Inferior ☐ Posterior

Hypertrophy, enlargement, and other ECG diagnosis

☐ Right Ventricular Hypertrophy
☐ Left Ventricular Hypertrophy
☐ Non-specific S-T segment abnormality
☐ Non-specific T –wave abnormality
☐ U-wave present
Atrial enlargement: ☐ Left ☐ Right ☐ Both
☐ Atrial fib ☐ Unknown

Comments_____
_____
_____

II. CORONARY HEART DISEASE EPISODE:

Chest discomfort? ☐ Yes ☐ No
If yes: ☐ Chest discomfort with exertion or excitement ☐ Chest discomfort when quiet or resting

Chest discomfort characteristics
Date of onset: _____Usual duration (minutes):_____Longest duration (minutes):_____
Location: ☐ Central Sternum and upper chest ☐ L up quadrant ☐ L Lower ribcage ☐ R chest ☐ Other/Unknown _____
Frequency (number in past month):_____ Frequency (number in past year):_____
Type: ☐ Pressure ☐ Sharp ☐ Dull ☐ Other/unknown_____
☐ Relief with Nitro glycerine in< 15 minutes ☐ Relief by rest in< 15 minutes ☐ Relief spontaneously in< 15 minutes
☐ Relief by other cause in< 15 minutes
Rapporteur evaluation
☐ Congestive heart failure
☐ Angina pectoris
☐ Coronary insufficiency
☐ Myocardial Infarction
☐ Cardiac dysrhythmia, other/palpitations
☐ Cardiac arrest
☐ Unknown
☐ Other _____

Comments_____
_____
_____

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

III. SYNCOPE EPISODE:

Faint or loss of consciousness

☐ Yes
☐ No
☐ Unknown

If yes:

Number of episodes in the past 2 years_____
Date of first episode _____/_____/_____
Usual duration of loss of consciousness (minutes) _____

Usual activity preceding event:

☐ None
☐ Exertion
☐ Rest
☐ Defecation/Micturition/cough
☐ Emotional upset
☐ Alcohol consumption
☐ Turning neck (eg. shaving)
☐ Postural change (eg. lying to standing)
☐ Recent medication change or ingestion
☐ Other, or combination (specify)_____
☐ Pain
☐ Illness (Specify)_____
☐ Unknown

Symptoms noted before event(s)

☐ Nausea/vomiting
☐ Warning signs (eg. Aura)
☐ Chest discomfort
  ☐ Shortness of breath
  ☐ Palpitations

Symptoms noted after event(s)

☐ Urinary/fecal incontinence
☐ Confusion
☐ Focal weakness (eg. arm, leg)
☐ Other (specify)
_____

Any injury caused by the event?

☐ Yes
☐ No
☐ Unknown

Was event observed?

☐ Yes
☐ No
☐ Unknown
Who observed event _____

Rapporteur evaluation:

Syncope:
☐ Yes
☐ No
☐ Unknown

If yes or no, please clarify origin
  ☐ Presyncope
  ☐ Cardiac syncope
  ☐ Vasovagal syncope
  ☐ Seizure disorder
  ☐ Unknown
  ☐ Other (specify):_____

IV. CEREBROVASCULAR EPISODE

Possible cerebrovascular episode? ☐ Yes ☐ No ☐ Unknown

If yes:

☐ Sudden Muscular weakness
☐ Sudden Speech difficulty
☐ Sudden visual defect
☐ Double vision
☐ Loss of vision in one eye
☐ Unconsciousness
☐ Numbness, tingling
☐ Unknown
Other _____

Rapporteur evaluation:

☐ Stroke
☐ Transient ischemic attack (TIA)
☐ Unknown

Onset:

Date: ____/___/___ Time: __: __ Duration _____or ☐ ongoing

☐ Active
☐ During sleep
☐ While awake
☐ Unknown

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

	CT OR MRI SCAN (HEAD) DATE _____ _____ _____ _____ ***Echocardiogram DATE*** _____ ☐ Trans-thoracic ☐ Trans-esophageal _____ _____ _____ ***Doppler Ultrasonography DATE*** _____ ☐ Carotideal ☐ Vertebral ☐ Transcranial _____ _____ _____ ***Neurology comments date*** _____ _____ _____ _____ _____

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

V. PERIPHERAL ARTERIAL/VENOUS EPISODE		
☐ Able to walk 50 m without help ☐ Needs help ☐ Can't walk ☐ Unknown	Cramping in calves or thighs ☐ Yes ☐ No ☐ Can't walk ☐ Unknown	Vascular symptoms: ☐ Right ☐ Left ☐ No ☐ Unknown ☐ Discomfort in calf while walking ☐ Discomfort in lower extremity (not calf) while walking ☐ Occurs with first steps ☐ After walking a while ☐ Related to rapidity of walking or steepness ☐ Forced to stop walking ☐ Time for discomfort to be relieved by stopping (minutes) _____ ☐ No relief with stopping ☐ Not applicable ☐ Number of days/month of lower limb discomfort _____

Rapporteur evaluation
Intermittent claudication ☐ yes ☐ No ☐ Unknown
Arterial Disease ☐ yes ☐ No ☐ Unknown
Deep Vein Trombosis ☐ yes ☐ No ☐ Unknown
Other
_____

Comments
_____
__

VI. Cardiovascular procedure		
	Date	**Result**
Exercise tolerance test		
Coronary arteriogram		
Coronary artery angioplasty		
Coronary bypass surgery		
Permanent pacemaker insertion		
Carotid artery surgery		
Thoracic aorta surgery		
Abdominal aorta surgery		
Femoral or lower extremity surgery		
Lower extremity amputation		
Valve surgery		

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

Other:		

SERIOUS ADVERSE CARDIOVASCULAR/CEREBROVASCULAR REACTION REPORT FORM

D.SUSPECT DRUG

19. SUSPECT DRUG(S) (include generic name and batch nº)		**25. DID REACTION ABATE AFTER STOPPING DRUG?** ☐YES ☐NO ☐NA
20. DAILY DOSE(S)	**21. ROUTE(S) OF ADMINISTRATION**	**26. DID REACTION REAPPEAR AFTER REINTRODUCTION?** ☐YES ☐NO ☐NA
22. INDICATION(S) FOR USE		
23. THERAPY DATES (from/to)	**24. THERAPY DURATION**	

E. CONCOMITANT THERAPY (Attach additional pages if necessary)

27. **IS PATIENT TAKING ANY CONCOMITANT MEDICATION:** ☐ Yes, as listed below ☐ No ☐ Unknown

List all medications (including contraceptives, over-the-counter (non-prescription) medicinal products and herbal products) taken by patient within the last month of onset of the ADR (except those used to treat the ADR)

MEDICATION (generic name)	DOSE	ROUTE	FREQUENCY	START DATE dd/mmm/yyyy	STOP DATE dd/mmm/yyyy	INDICATION

G. OTHER INFORMATION

28. **PLEASE DESCRIBE HERE OTHER RELEVANT INFORMATION**

_____

_____

_____

29. **CAUSAL RELATIONSHIP TO INVESTIGATIONAL PRODUCT**: (Rapporteur's Assessment)

☐ Not related
☐ Unlikely
☐ Possible
☐ Probable
☐ Definite

_____ **RAPPORTEUR'S SIGNATURE**	__ __ / __ __ __ / __ __ __ __ **DATE** (dd/mmm/yyyy)

Annex 4.3 Serious adverse cutaneous reaction report form

SERIOUS ADVERSE CUTANEOUS REACTION REPORT FORM

1. IDENTIFICATION Nº/ COUNTRY	**2.** DRUG: **4.** CLINICAL TRIAL **L** ☐ No ☐ Yes Protocol nº: Centre nº: Patient nº	**3.** DATE OF THIS REPORT: (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

A. GENERAL INFORMATION

TYPE OF REPORT: ☐ Initial ☐ Follow-Up # _____

5. **RAPPORTEUR**

Name: _____ Phone number: _____

Address: _____ Email: _____

_____

_____

B. PATIENT INFORMATION

	7. **DATE OF BIRTH** (dd/mmm/yyyy): __ __ / __ __ / __ __		9. **SEX**: ☐ Male ☐ Female		**11. HEIGHT** _____ (cm) **WEIGHT** _____(kg)	12. **OCCUPATION** _____

13. MEDICAL HISTORY (If Yes, please specify)

Clinically relevant family history?	No ☐	Yes ☐
History of relevant atopy?	No ☐	Yes ☐
Allergic reactions? (To what drug?)	No ☐	Yes ☐
Allergic rhinitis?	No ☐	Yes ☐
Previously-identified sensitivity to structurally-related antiepileptic drugs (i.e. carbamazepine or oxcarbazepine)?	No ☐	Yes ☐

SERIOUS ADVERSE CUTANEOUS REACTION REPORT FORM

13. MEDICAL HISTORY (If Yes, please specify)			
Disease/disorder			Clinically significant?
Respiratory	No ☐	Yes ☐	Yes ☐ No ☐
Gastrointestinal	No ☐	Yes ☐	Yes ☐ No ☐
Renal	No ☐	Yes ☐	Yes ☐ No ☐
Hepatic	No ☐	Yes ☐	Yes ☐ No ☐
Haematological	No ☐	Yes ☐	Yes ☐ No ☐
Lymphatic	No ☐	Yes ☐	Yes ☐ No ☐
Neurological	No ☐	Yes ☐	Yes ☐ No ☐
Cardiovascular	No ☐	Yes ☐	Yes ☐ No ☐
Psychiatric	No ☐	Yes ☐	Yes ☐ No ☐
Musculoskeletal	No ☐	Yes ☐	Yes ☐ No ☐
Genitourinary	No ☐	Yes ☐	Yes ☐ No ☐
Immunological	No ☐	Yes ☐	Yes ☐ No ☐
Endocrine	No ☐	Yes ☐	Yes ☐ No ☐
Dermatological	No ☐	Yes ☐	Yes ☐ No ☐
Connective tissue	No ☐	Yes ☐	Yes ☐ No ☐
Other	No ☐	Yes ☐	Yes ☐ No ☐

SERIOUS ADVERSE CUTANEOUS REACTION REPORT FORM

C. ADVERSE DRUG REACTION (ADR) INFORMATION

14. **ADR TERM** (Signs/symptoms if no diagnosis made)	15. **ONSET DATE** (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __	16. **OFFSET DATE** (dd/mmm/yyyy) __ __ / __ __ __ / __ __ __ __ OR ☐ ongoing

17. **DESCRIPTION**: (include relevant tests and dates, Continue on last page or add additional page(s) if necessary):

_____
_____
_____
_____
_____

CHECK IF ATTACHED: ☐ Discharge report ☐ Autopsy report ☐ Laboratory / other test results ☐ Photographs

18. **TYPE OF SKIN DISORDER** (FIND IMPORTANT RECOMMENDATION ON PAGE 5)

☐ Macular or maculopapular rash
☐ Scarlatiniform rash
☐ Exfoliative dermatitis
☐ Bullous or vesicular eruption
Specify: ☐ Fixed drug eruption
☐ Erythema multiforme (target lesions)
☐ Steven-Johnson syndrome
☐ Toxic Epidermal Necrolysis (TEN)
☐ Other:
☐ Purpura (Platelet count needed)
☐ Palpable purpura ☐ Necrotic purpura

☐ Lichenoid / Lichen Planus like reactions
☐ Pruritus alone
☐ Contact dermatitis or eczematiform eruption
☐ Urticaria
☐ Cutaneous angioedema
☐ Mucosal angioedema
☐ Pigmentation change:
☐ Hyperpigmentation ☐ Hypopigmentation
☐ Dyspigmentation ☐ Other:
☐ Alopecia

☐ Other skin disorders, *(specify)*:

19. **DISTRIBUTION OF LESIONS**:

☐ Localized ☐ Disseminated

Number of lesions
☐ < 10
☐ 10 to 30
☐ > 30

Main location:
☐ Mucosal, specify:
☐ Nail/hair, specify:

20. **HLA GENOTYPE**:(FIND IMPORTANT RECOMMENDATION ON PAGE 5)

Please include information/*attach report:*

HLA-A*3101:_____ HLA-B*1502:_____ other:_____

21. **ASSOCIATED SIGNS AND SYMPTOMS**

☐ Pruritus
☐ Burning or pain
☐ Edema
☐ Infection
☐ Oozing
☐ Hypotension
☐ Anaphylactic shock
☐ Dyspnoea
☐ Tachycardia
☐ Fever
☐ Arthralgia/myalgia
☐ Nodes enlargement
☐ Sibilant wheeze
☐ Visceral involvement:
☐ Kidney
☐ GI trac
☐ Nerves
☐ Others:
☐ Other, specify:

22. EVIDENCE OF VIRAL INFECTION:

	No	Yes	Not done
EBV	☐	☐	☐
Hepatitis B virus	☐	☐	☐
CMV	☐	☐	☐
Herpes	☐	☐	☐
HIV	☐	☐	☐
Other:	☐	☐	☐

23. **IS PHOTOSENSITIVITY SUSPECTED**? ☐ No ☐ Yes

Localization of lesion:

24. **SKIN BIOPSY** ☐ No ☐ Yes
Result (*attach report*)

SERIOUS ADVERSE CUTANEOUS REACTION REPORT FORM

☐ Face ☐ Neck ☐ Hands/forearms ☐ Legs/Feet ☐ Other specify Intensity of solar exposure: ☐ High ☐ Mild ☐ Low	**IMMUNOFLUORESCENT STAINING** ☐ No ☐ Yes Result (*attach report*)

25. **SEVERITY** (Intensity): ☐ Mild ☐ Moderate ☐ Severe ☐ Not applicable

26.. **EVENT ABATED AFTER INVESTIGATIONAL PRODUCT WAS REDUCED OR WITHDRAWN?** ☐ Yes ☐ No ☐ Not applicable

27. **EVENT REAPPEARED AFTER INVESTIGATIONAL PRODUCT REINTRODUCTION?** ☐ Yes ☐ No ☐ Not applicable

28. SERIOUSNESS
☐ Non-serious
☐ Serious. Why? (Check one or more):

- ☐ fatal
- ☐ life-threatening
- ☐ persistent or significant disability/incapacity
- ☐ congenital anomaly/birth defect
- ☐ required hospitalization
  Admission date __ __ / __ __/ __ __ __ __ Discharge date __ __ / __/ __ __ __ _
- ☐ other medically important condition

D.SUSPECT DRUG

29. SUSPECT DRUG(S) (include generic name and batch nº)

30. DAILY DOSE(S)	**31. ROUTE(S) OF ADMINISTRATION**
32. INDICATION(S) FOR USE	
33. THERAPY DATES (from/to)	**34. THERAPY DURATION**
35. DID REACTION ABATE AFTER STOPPING DRUG? ☐YES ☐NO ☐NA	**36. DID REACTION REAPPEAR AFTER REINTRODUCTION?** ☐YES ☐NO ☐NA

E. CONCOMITANT MEDICATION (Attach additional pages if necessary)

37. **IS PATIENT TAKING ANY CONCOMITANT MEDICATION:** ☐ Yes, as listed below ☐ No ☐ Unknown

List all medications (including contraceptives, over-the-counter (non-prescription) medicinal products and herbal products) taken by patient within the last month of onset of the ADR (except those used to treat the ADR)

MEDICATION (generic name)	DOSE	ROUTE	FREQUENCY	START DATE dd/mmm/yyyy	STOP DATE dd/mmm/yyyy	INDICATION

F. OTHER INFORMATION

38. **PLEASE DESCRIBE OTHER RELEVANT INFORMATION**

_____

_____

_____

_____

SERIOUS ADVERSE CUTANEOUS REACTION REPORT FORM

39. **CAUSAL RELATIONSHIP TO INVESTIGATIONAL PRODUCT**: (Rapporteur's Assessment)

☐ Not related
☐ Unlikely
☐ Possible
☐ Probable
☐ Definite

RECOMMENDATION FOR SEVERE SKIN REACTIONS:

HLA-B* 1502 allele has been associated with Carbamazepine-induced Steven's Johnson Syndrome (SJS) and Toxic Epidermal necrolysis (TEN) in individuals of Han Chinese and Thai origin. HLA-A*3101 allele was associated with Carbamazepine-induced hypersensitivity reactions among subjects of Northern European ancestry.

Such a relation has not been established with Eslicarbazepine Acetate, however in order to get further data, the Committee for Medicinal Products for Human Use (CHMP) recommends that whenever possible, patients experiencing severe cutaneous reactions, including SJS and TEN following exposure to eslicarbazepine acetate be genotyped for HLA-B*1502 and HLA-A*3101 genotypes.

If such information is available, please complete section 20.

_____ **RAPPORTEUR'S SIGNATURE**	__ __ / __ __ __ / __ __ __ __ **DATE** (dd/mmm/yyyy)

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

[redacted]