



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eslicarbazepine acetate

Proprietary Product Name: Zebinix

Sponsor: Maxx Pharma Pty Ltd

September 2021

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARD	Average risk difference
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
AST	Aspartate aminotransferase
BMI	Body mass index
CGI	Clinical Global Impression
CI	Confidence interval
CL _{CR}	Creatinine clearance
CMI	Consumer Medicines Information
CR	Controlled release (formulation)
CYP	Cytochrome P450
DLP	Data lock point
EU	European Union
FAS	Full analysis set
GABA	Gamma-aminobutyric acid
GGT	Gamma glutamyltransferase
GVP	Good Pharmacovigilance Practices
HRQoL	Health-related quality of life
LS	Least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
OLE	Open label extension

Abbreviation	Meaning
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
POS	Partial-onset seizure(s)
PSUR	Periodic safety update report
QOLIE-31	Quality of Life in Epilepsy-31 Inventory
RCT	Randomised clinical trial
RMP	Risk management plan
SOC	System Organ Class
SPC	Summary of product characteristics
T ₄	Thyroxine
TEAE	Treatment-emergent adverse event
USA	United States of America
VGSC	Voltage-gated sodium channel
VNS	Vagal nerve stimulation

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product name:</i>	Zebinix
<i>Active ingredient:</i>	Eslicarbazepine acetate
<i>Decision:</i>	Approved
<i>Date of decision:</i>	10 May 2021
<i>Date of entry onto ARTG:</i>	18 May 2021
<i>ARTG numbers:</i>	335289 and 335290
<i>, Black Triangle Scheme:¹</i>	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
<i>Sponsor's name and address:</i>	Maxx Pharma Pty Ltd Level 11, 500 Collins Street Melbourne, VIC, 3000
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	200 mg and 800 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	200 mg: 20 and 60 tablets 800 mg: 20, 30, 60, 90 and 180 tablets
<i>Approved therapeutic use:</i>	<i>Zebinix is indicated as:</i> <ul style="list-style-type: none"><i>monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;</i><i>adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.</i>
<i>Route of administration:</i>	Oral

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:**Use in adults:**

Zebinix may be taken as monotherapy or added to existing anticonvulsant therapy. The recommended starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response, the dose may be increased to 1,200 mg once daily. Some patients on monotherapy regimen may benefit from a dose of 1,600 mg once daily (see Section 5.1 Pharmacodynamic properties in the Product Information).

Use in the paediatric population*Children above 6 years of age:*

The recommended starting dose is 10 mg/kg/day once daily. 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 1,200 mg once daily (see Section 5.1 Pharmacodynamic properties in the Product Information).

Children with a body weight of 60 kg or more:

Children with a body weight of 60 kg or more should be given the same dose as for adults.

For further information regarding dosage, refer to the Product Information.

Pregnancy category:

D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Maxx Pharma Pty Ltd (the sponsor) to register Zebinix (eslicarbazepine acetate) 200 mg and 800 mg, tablet for the following proposed indication:

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

Epilepsy is a common disorder of the brain affecting 1 to 2% of the world's population. Epilepsy is characterised by seizures, which are episodes of abnormal, synchronous neuronal firing usually accompanied by a reduction in awareness or by focal neurological symptoms. Seizures are usually classified into focal seizures, which begin in one part of the brain, or primary generalised seizures, which involve the whole brain network from the onset of the seizure. Focal seizures may spread, eventually involving the whole brain as the seizure progresses and these are known as secondarily generalised seizures. Focal seizures are the most common form of seizures, though the seizures may spread so rapidly that the initial focal phase is not clinically apparent. A person is considered to have epilepsy when two or more unprovoked seizures occur that can't be explained by a medical condition such as fever or substance withdrawal.

Each distinct form of epilepsy has its own natural history and response to treatment. This diversity probably reflects the many different underlying causes of epilepsy and the variety of epilepsy syndromes in which the clinical and pathological characteristics are distinctive and suggest a specific underlying etiologic mechanism.

Antiepileptic drug (AED) therapy, the mainstay of treatment for most patients, has four goals: to eliminate seizures or reduce their frequency to the maximum degree possible; to evade the adverse effects associated with long term treatment; to aid patients in maintaining or restoring their usual psychosocial and vocational activities; and, to aid patients in maintaining a normal lifestyle. Most existing anticonvulsants work by inhibiting sodium channels, by enhancing or mimicking the inhibition mediated by endogenous gamma-aminobutyric acid (GABA) or by inhibiting the release of excitatory neurotransmitters. Inhibiting voltage-gated calcium channels can also be useful for some seizure types. Despite the rapid development of a range of AEDs, seizures are not adequately controlled in a third of cases, no disease-modifying therapies exist, and comorbidities are a major burden on quality of life. There is an urgent demand to address the unmet clinical needs of patients, specifically, treatments for drug resistant seizures, treatments with improved tolerability, and treatments that prevent or attenuate epileptogenesis.

In Australia there are over 20 AEDs used to treat seizures. The AEDs prescribed are often selected on the basis of the seizure type, age, gender and side effects. AEDs may be prescribed as tablets, syrups and liquids.

Carbamazepine is one of the most important AEDs, but its effectiveness is compromised by a complicated metabolism and relatively high incidence of adverse events (AEs). The toxic effects are thought to be at least partly due to the formation of a meso-epoxide metabolite (carbamazepine-10, 11-epoxide) via the inducible cytochrome P450 (CYP);² isoform CYP3A. In order to circumvent the formation of the epoxide metabolite, oxcarbazepine was developed as a second generation keto-analogue of carbamazepine. Unlike carbamazepine, oxcarbazepine does not undergo inducible CYP3A4-mediated oxidative metabolism. Instead, oxcarbazepine undergoes rapid pre-systemic metabolic 10-keto reduction to 10-hydroxy-carbazepine. Eslicarbazepine (acetate) is also part of the dibenzazepine-carboxamide family, like carbamazepine and oxcarbazepine. The sponsor

² **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

asserts that eslicarbazepine presents a molecular variation to these, since it presents a hydroxy group rather than a keto group in the 10 position of the ring which results in functional differences from carbamazepine and oxcarbazepine. This molecular variation, seen in eslicarbazepine results in differences in metabolism thus reducing enantiomer impurities (without the loss of pharmacological activity) giving a lower potential for drug-drug interactions, improved tolerability, and ease of use (once daily dosing and a simple titration regimen).

Eslicarbazepine is a voltage-gated sodium channel (VGSC) blocker that competitively interacts with Site 2 of the inactivated state of VGSC. It stabilises the inactive state of VGSCs, allowing for less sodium to enter neural cells, which leaves them less excitable.

In addition to carbamazepine and oxcarbazepine, there are several other AEDs on the market (for example, felbamate, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, pregabalin, topiramate, tiagabine, valproate, and zonisamide). Somnolence, dizziness, fatigue, headache, nausea and vomiting are the most common type of events with these drugs. In addition, psychiatric events such as abnormal thinking, depression, and psychosis are common to several of these AEDs. Furthermore, the majority of these drugs require administration several times a day and involve complex and long term titration schemes. Eslicarbazepine is proposed to have a favourable toxicity profile and provide improved convenience and compliance.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) (on 21 April 2009), the United States of America (USA) (on 8 November 2013), Canada (on 8 July 2014) and Switzerland (on 2 April 2020).

Table 1, shown below, summarises these applications and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	26 March 2008	Approved on 21 April 2009	<i>Monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;</i> <i>Adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalization.</i>
United States of America	29 March 2009	Approved on 8 November 2013	<i>Treatment of partial-onset seizures in patients 4 years of age and older.</i>

Region	Submission date	Status	Approved indications
Canada	6 August 2009	Approved on 8 July 2014	<p><i>Monotherapy in the management of partial-onset seizures in adult patients with epilepsy. All patients who participated in the monotherapy trial were newly or recently diagnosed with epilepsy.</i></p> <p><i>Adjunctive therapy in the management of adults, and children above 6 years of age, with partial-onset seizures who are not satisfactorily controlled with conventional therapy.</i></p>
Switzerland	17 December 2018	Approved on 2 April 2020	<p><i>Monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;</i></p> <p><i>Adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalization.</i></p>

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-01850-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 June 2020
First round evaluation completed	20 November 2020

Description	Date
Sponsor provides responses on questions raised in first round evaluation	19 January 2021
Second round evaluation completed	5 May 2021
Delegate's Overall benefit-risk assessment	26 April 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	10 May 2021
Completion of administrative activities and registration on the ARTG	18 May 2021
Number of working days from submission dossier acceptance to registration decision*	196

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guideline referred to by the Delegate is given below:

- European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), 22 July 2010. Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders (CPMP/EWP/566/98 Rev. 2/Corr).

Quality

Approval is recommended from a pharmaceutical chemistry and quality control perspective.

There are no products currently registered on the Australian Register of Therapeutic Goods (ARTG) containing eslicarbazepine (acetate).

Each Zebinix 200 mg uncoated tablet contains 200 mg eslicarbazepine and appears as a white oblong tablets, engraved with 'ESL 200' on one side and scored on the other side, with a length of 11 mm.

Each Zebinix 800 mg uncoated tablet contains 800 mg eslicarbazepine and appears as a white oblong tablets, engraved with 'ESL 800' on one side and scored on the other side, with a length of 19 mm.

The score line for both tablet strengths is a functional one.

The tablets are to be packaged in polyvinyl chloride/aluminium blisters in pack sizes of 20 and 60 tablets for the 200 mg strength and 20, 30, 60, 90 and 180 tablets (as two packs of 90) for the 800 mg strength.

The maximum recommended daily dose for eslicarbazepine is 1600 mg.

Nonclinical

In vitro examinations of potential pharmacokinetic (PK) drug interactions were limited; low concentrations were used in the CYP 450 assays,² and no studies were submitted to assess the potential of eslicarbazepine to inhibit transporters. The sponsor is encouraged to conduct these assays and submit the reports in a subsequent submission.

Pregnancy Category B3,³ as the sponsor proposes, is not supported. Pregnancy Category D;⁴ is recommended based on malformations seen in three species.

The overall safety profile of eslicarbazepine (acetate) was similar to that of oxcarbazepine.

There are no nonclinical objections to the registration of eslicarbazepine (Zebinix) for the proposed monotherapy indication. The toxicity of eslicarbazepine with possible combination therapies was not examined in the nonclinical module. Given the similarity of toxicity and mechanism of efficacy with oxcarbazepine. Eslicarbazepine should not be used with oxcarbazepine. The draft PI should be amended as directed.

Clinical

The clinical dossier consisted of the following studies:

- 26 Phase I clinical pharmacology studies
- 3 pivotal Phase III studies: Study BIA-2093-301 (abbreviated as Study 301), Study BIA-2093-302 (Study 302) and Study BIA-2093-303 (Study 303).
- Other clinical Phase II/III studies: Study BIA-2093-201 (Study 201), Study BIA-2093-202 (Study 202), Study BIA-2093-208 (Study 208), Study BIA-2093-304 (Study 304), Study BIA-2093-305 (Study 305), Study BIA-2093-311 (Study 311), and Study BIA-2093-401 (Study 401).

Pharmacology

Pharmacokinetics

Eslicarbazepine (acetate) has been characterised as having rapid and complete oral absorption. Pharmacokinetic (PK) studies show predictable metabolism and renal excretion. The clinical dossier is sufficient to justify once daily dosing as adequate compared to twice daily dosing. There are adequate studies to inform recommendations around dosage adjustment in patients with renal failure, the main method of excretion of the major active metabolite of eslicarbazepine. There were few clinically significant drug interactions. PK studies in healthy subjects and target population show similar rates, extent of absorption, metabolism and excretion which are adequately addressed in the proposed PI.

Pharmacodynamics

- Primary pharmacodynamic (PD) effects are satisfactorily elucidated in the clinical development program.

³ **Pregnancy Category B3:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

⁴ **Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- On the basis of the nonclinical dossier, the one gap is the potential for eslicarbazepine to delay gastric emptying, which has not been evaluated in humans. However, the lack of this data does not require specific investigation but rather should be mentioned in the PI.

Dose selection

The doses used to evaluate the efficacy of eslicarbazepine (Zebinix) in the Phase II/III trials were derived from the Phase I studies and one Phase II study which showed therapeutic properties and an acceptable safety profile of 800 mg and 1200 mg Zebinix as adjunctive therapy in a once daily regimen, and a smaller treatment response for the 400 mg dose. The Phase III studies were planned to define the dose recommendations to be included in the summary product characteristics (SPC). Based on these results, Zebinix 400 mg (except in Study 303), 800 mg and 1200 mg were investigated in the Phase II and III studies in the proposed indication.

The clinical evaluator concluded that efficacy analyses concerning simple partial and complex partial seizures demonstrated a relevant effect of the 800 mg and 1200 mg dose as adjunctive therapy. No significant efficacy benefits demonstrated for 1600 mg in monotherapy studies above 1200 mg. There appears to be a dose dependent relationship with treatment-emergent adverse events (TEAE) in both adjunctive therapy and monotherapy adult studies. Paediatric data suggest a dose dependent effect of efficacy but not safety variables.

Efficacy

Overview of efficacy studies

The three pivotal studies (Studies 301, 302 and 303) were similar in design (see Table 3).

Table 3: Studies 301, 302 and 303 Study design and treatment regimen

Study	Number of subjects randomised	Study design	Treatment regimen
301	402	Part I: A 26 week, parallel group, randomised, placebo-controlled study (22 weeks in Study 302) with: <ul style="list-style-type: none"> an 8 week baseline period (in Study 301: single blind placebo period); a 2 week double blind titration period; a 12 week double blind maintenance period; and a 4 week double blind tapering-off period (not in Study 302) Part II: An optional, one year, open label extension for subjects who had completed Part I.	Part I: <ul style="list-style-type: none"> Placebo Daily doses of eslicarbazepine acetate: <ul style="list-style-type: none"> Studies 301 + 302 = 400, 800 or 1200 mg (once daily) Study 303 = 800 or 1200 mg (once daily) Part II: A starting dose of 800 mg eslicarbazepine acetate once daily that could be titrated up or down at 400 mg intervals between 400 and 1200 mg.
302	395		
303	253		

The only major differences between the three studies in the Part I study design were the doses of eslicarbazepine given and differences in the study periods and titration regimens:

- There were three eslicarbazepine dose groups (400 mg, 800 mg or 1200 mg once daily) in Studies 301 and 302, but only two eslicarbazepine dose groups (800 mg or 1200 mg once daily) in Study 303.
- The baseline period was observational in Studies 302 and 303 and single blind placebo in Study 301.
- In Study 302 there was no tapering-off period.
- All three studies used slightly different titration and tapering-off regimens.

Objectives

The primary objective was to evaluate the efficacy of eslicarbazepine administered once daily compared with placebo as adjunctive therapy in patients with refractory partial epilepsy.

The secondary objectives were:

- to evaluate the safety and tolerability of eslicarbazepine at once daily doses in comparison to placebo;
- to evaluate the safety and tolerability of eslicarbazepine at doses titrated to an efficacy or safety endpoint over a one-year open label period;
- to assess the maintenance of therapeutic effects of eslicarbazepine over a the maintenance period preceded by a two week titration period and followed by a tapering-off period and over a one year open label period;
- to assess the drug-drug PK interactions between eslicarbazepine and concomitant AEDs over the double blind and open label parts of the study; and
- to assess the health-related quality of life and depressive symptoms over the double blind and open label parts of the study.

Key inclusion criteria for each of the three studies were:

At Visit 1 (screening), subjects must have:

- been 18 years or older;
- had a documented diagnosis of simple or complex partial seizures with or without secondary generalisation for at least 12 months prior to screening;
- had at least four partial seizures in each four week period during the last eight weeks prior to screening;
- been currently treated with one or two AEDs (any except oxcarbazepine and felbamate), in a stable dose regimen for at least two months prior to screening (subjects using vigabatrin should have been on this medication for at least one year with no deficit in visual field identified, and a confirmatory test should be available within one month before study entry; if present, vagal nerve stimulation (VNS) was considered an AED, that is, only one concomitant AED was allowed in subjects with VNS);
- in Study 302, the number of allowed concomitant AEDs was extended to three AEDs by amendment.

At Visit 2 (randomisation), subjects must have:

- had at least four partial seizures in each four week period of the eight week baseline period prior to randomisation (documented in a diary) and no seizure free interval exceeding 21 consecutive days;
- satisfactorily completed diaries by themselves or their caregiver;
- satisfactorily complied with the study requirements during the baseline period.

Key exclusion criteria for each of the three studies included if a subject had:

- only simple partial seizures with no motor symptomatology (classified as A2-4 according to the International Classification of Epileptic Seizures) that were not video-electroencephalogram documented;
- primary generalised epilepsy;
- known rapid progressive neurological disorder;
- a history of status epilepticus or cluster seizures (three or more seizures within 30 minutes) within the three months prior to screening;
- seizures of psychogenic origin within the last two years;
- a history of schizophrenia or suicide attempt;
- exposure to felbamate or oxcarbazepine within one month of screening;
- exposure to benzodiazepines on more than an occasional basis (except when used chronically as AED);
- known hypersensitivity to carbamazepine, oxcarbazepine, or chemically-related substances.
- second or third degree atrioventricular blockade not corrected with a pacemaker;
- relevant clinical laboratory abnormalities (for example, $\text{Na}^+ < 130 \text{ mmol/L}$, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal, white blood cell count $< 3,000 \text{ cells/mm}^3$);
- an estimated creatinine clearance (CL_{CR}) $< 50 \text{ mL/min}$.

Study treatment

During the eight week baseline period of Study 301, placebo was administered once daily in a single blind fashion, which should allow for an accounting of the number of seizures under placebo treatment.

In Studies 302 and 303, no study treatment was administered during baseline. At the end of the baseline period, subjects who met the selection criteria were randomly assigned to one of the following treatment groups, study medication was taken without regard to meals:

Table 4: Studies 301, 302 and 303 Subjects randomisation and corresponding treatment groups assigned

Studies 301 and 302	Study 303
Randomisation ratio: 1:1:1:1	Randomisation ratio: 1:1:1
Group 1: ESL 1200 mg Group 2: ESL 800 mg Group 3: ESL 400 mg Group 4: placebo	Group 1: ESL 1200 mg Group 2: ESL 800 mg Group 4: placebo

ESL = eslicarbazepine acetate.

Dosing Schedule

Table 5: Studies 301, 302 and 303 Dosing schedule

Group	Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
Group 1: 1200 mg	301	Placebo	Week 1: 400 mg Week 2: 800 mg	1200 mg	Week 15: 800 mg Week 16: 400 mg Weeks 17/18: placebo
	302	No treatment	800 mg	1200 mg	Not applicable
	303	No treatment	600 mg	1200 mg	Weeks 15/16: 600 mg Weeks 17/18: placebo
Group 2: 800 mg	301	Placebo	Week 1: 400mg Week 2: 800mg	800 mg	Week 15: 800 mg Week 16: 400 mg Weeks 17/18: placebo
	302	No treatment	800 mg	800 mg	Not applicable
	303	No treatment	400 mg	800 mg	Weeks 15/16: 400 mg Weeks 17/18: placebo
Group 3: 400 mg	301	Placebo	400 mg	400 mg	Week 15/16: 400 mg

Group	Study	Baseline (V1 to V2)	Titration (V2 to V3)	Maintenance (V3 to V5)	Tapering-off (V5 to V6)
					Weeks 17/18: placebo
	302	No treatment	400 mg	400 mg	Not applicable
	303	Not applicable			
Group 4: placebo	301	Placebo	Placebo	Placebo	Placebo
	302	No treatment	Placebo	Placebo	Not applicable
	303	No treatment	Placebo	Placebo	Placebo

V = visit.

Efficacy variables

Primary variable

In all three pivotal studies, the primary efficacy endpoint was:

- seizure frequency over the 12 week maintenance period in Part I of the study, standardised to a 'frequency per four weeks' unit.

Secondary variables

Secondary variables included:

- Proportion of responders (that is., patients with a $\geq 50\%$ reduction in seizure frequency during the 12 week maintenance period compared with the eight week baseline period)
- Seizure frequency per week for each week of the baseline, titration, maintenance, and tapering-off periods (the latter except Study 302, which had no tapering-off period)
- Distribution of seizure reduction (< 50%, 50% to 75%, or > 75% seizure reduction)
- Proportion of seizure-free patients (100% seizure reduction)
- Proportion of patients with a 25% or greater exacerbation in seizure frequency compared to Baseline
- Seizure frequency by seizure type
- Seizure frequency as a function of Study BIA 2-194 plasma levels at Visit 5
- Treatment retention time (time to withdrawal due to lack of efficacy or adverse events) during Part I of the study
- Clinical Global Impressions (CGI)
- Responses to the Quality of Life in Epilepsy-31 Inventory (QOLIE-31);⁵

⁵ The **Quality of Life in Epilepsy-31 Inventory (QOLIE-31)** is a validated scale derived from the long form original long-form QOLIE-89. The QOLIE-31 includes 31 self-reported items clustered in seven multi-item scales centred on the following domains: overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects, seizure worry, and social functioning. A scoring system is available for each item (from 0 to 3 or from 0 to 6).

- Symptoms of depression based on Montgomery-Åsberg Depression Rating Scale (MADRS).⁶

All pivotal studies were randomised and double blind. The randomisation procedure appears adequate. In Studies 301 and 302, patients were randomised in a 1:1:1:1 ratio to placebo, eslicarbazepine 400 mg/day, eslicarbazepine 800 mg/day or eslicarbazepine 1200 mg/day, respectively. In Study 303, patients were randomised in a 1:1:1 ratio to placebo, eslicarbazepine 800 mg/day or eslicarbazepine 1200 mg/day, respectively.

Conclusions

Adult population

Adjunctive therapy in refractory epilepsy

The primary efficacy analysis of seizure frequency per four week period during the maintenance period demonstrated statistically significant and consistent results across the four trials (Studies 301 to 304) for both eslicarbazepine (acetate) at 800 mg and 1,200 mg compared with placebo, except for one comparison: eslicarbazepine 800 mg versus placebo in Study 304. However, the proportion of responders (proportion of patients with seizure frequency reduction of 50% or more) can also be considered a clinically useful outcome. In this respect, approximately 30% to 40% of patients demonstrated a $\geq 50\%$ reduction in seizures and all findings were statistically significant compared with placebo, except in two instances when eslicarbazepine 800 mg was compared with placebo in Studies 303 and 304.

Numbers needed to treat to obtain one responder were eight with eslicarbazepine 800 mg, and ranged from five to seven with eslicarbazepine 1,200 mg. The percentage of responders seen in the included trials is in keeping with what is seen in randomized placebo-controlled trials with other AEDs used in this clinical setting.

Seizure frequency was also evaluated according to seizure types in Studies 302, 303, and 304. Across the three trials, findings were statistically significant for eslicarbazepine 1,200 mg compared with placebo for patients with complex partial seizures. Findings were statistically significant for eslicarbazepine 800 mg compared with placebo, and for eslicarbazepine 1,200 mg compared with placebo for patients with simple partial seizures in Study 302, but not in Studies 303 and 304. For all treatment groups in all three trials, there were no statistically significant differences in seizure frequency for patients with secondarily generalised seizures. These findings must be interpreted in light of the fact that sample sizes for each subgroup were relatively small and P-values are descriptive only.

While quality of life was assessed in the included trials using QOLIE-31, there were no statistically significant differences between eslicarbazepine and placebo. These findings were corroborated with CGI-I score, for which there was also no statistically significant differences between eslicarbazepine and placebo. For the majority of patients, there was no change or minimal improvement in CGI. No test of statistical significance was done for between group comparisons. It is unclear why the reductions in seizure frequency with eslicarbazepine did not translate into improvements in health-related quality of life (HRQoL) on a disease specific instrument such as the QOLIE-31, although benefits on HRQoL were also not apparent in trials of perampanel and lacosamide. The higher

⁶ The **Montgomery-Åsberg Depression Rating Scale (MADRS)** is a validated scale consisting of 10 items evaluating core symptoms of depression. Nine of the items are based upon patient report, and one is on the rater's observation during the rating interview. MADRS items are rated from 0 to 6 continuum (0 = no abnormality, 6 = severe). The MADRS addresses core mood symptoms such as sadness, tension, reduced appetite or sleep, pessimistic thoughts, and suicidal thoughts.

incidence of adverse effects in the eslicarbazepine groups may partially explain this finding.

In the one year open label extension (OLE) period, 2.5% of patients achieved seizure free status in Studies 302 and 303, while 37.2% and 52.6% of patients had a 50% or greater reduction in seizure frequency, respectively (results not reported for Study 301). In all three OLE trials, patients had statistically significant improvements from Baseline in the QOLIE-31 overall scores of between 2.1 points and 6.7 points. It should be noted that 20% to 30% of patients who entered the extension trials discontinued treatment before the end of the one year period due to withdrawal of consent, lack of efficacy, or the occurrence of unacceptable adverse events. Moreover, it is possible that patients in the randomised clinical trials (RCTs) who found eslicarbazepine treatment to be tolerable and efficacious were more likely to enrol in the extension trials. Over time, it is likely that the remaining cohort increasingly represented patients who had the greatest benefit and lowest incidence of adverse events because such patients self-selected to continue treatment in the OLE trials. Hence, the reduction in seizures and improvements in HRQoL observed with eslicarbazepine is likely overestimated in these studies.

The monotherapy Study 202 provides useful data supporting efficacy for monotherapy use of eslicarbazepine in partial epilepsy. Supportive evidence is provided from Studies 045 and 046 although the study design limits interpretation of this data. Compared to an appropriate active comparator, non-inferiority is demonstrated although the evaluator notes a trend to carbamazepine controlled-release (CR) formula being more efficacious.

Based on the analysis of covariance (ANCOVA) model of the integrated analysis of Studies 301 to 303, no effect was seen on the efficacy of eslicarbazepine when given concomitantly with carbamazepine, lamotrigine, or valproic acid.

Monotherapy

The primary objective of Study 311 was to demonstrate that monotherapy with eslicarbazepine (acetate) was non-inferior to monotherapy with controlled release carbamazepine in adults (≥ 18 years) with newly diagnosed epilepsy experiencing partial-onset seizures (POS). Inclusion and exclusion criteria for this study were generally adequate in order to identify a study population in line with the proposed target population of the claimed monotherapy indication. The study was designed with stepwise fixed dose increments based on individual response at three different dose levels: dose Level A (eslicarbazepine 800 mg once daily, carbamazepine-CR 200 mg twice daily), Level B (eslicarbazepine 1200 mg once daily or carbamazepine-CR 400 mg twice daily) and Level C (eslicarbazepine 1600 mg once daily or carbamazepine-CR 600 mg twice daily). Whereas eslicarbazepine dose Levels A and B in Study 311 were within the dose range currently approved for eslicarbazepine adjunctive treatment of adults with POS, the highest dose level, 1600 mg eslicarbazepine once daily, exceeded the maximum approved dose for add-on therapy (1200 mg once daily). See further discussion on dose recommendations below. The choice of carbamazepine-CR as the active comparator is agreed by the evaluator and appropriate for the population studied. Carbamazepine is approved for this as first choice treatment for POS in Australia and the controlled release formulation allows more stable plasma levels of the drug, avoiding peaks in plasma concentration and resulting in an overall better tolerability. Thus, it can be regarded as the active comparator of choice. Furthermore, the chosen dose levels of carbamazepine-CR were within the approved dose range of carbamazepine, in accordance with the most commonly used doses in clinical practice and in line with published literature, which suggests that the majority of subjects with newly diagnosed epilepsy respond to their first AED at a low dose.

The primary efficacy endpoint was the proportion of subjects who were seizure free for the entire 26 week evaluation period at the last evaluated dose level. Subjects who

dropped out during this 26 week period were considered as non-seizure free in the primary efficacy analysis. Seizure freedom rates were also evaluated after one year of treatment at the last evaluated dose level (secondary endpoint). Non-inferiority of eslicarbazepine to carbamazepine-CR was considered demonstrated if the one-sided 97.5% confidence interval (CI) for the absolute difference in proportions did not exceed the pre-specified non-inferiority margin of -12%. This would appear appropriate on the basis of currently accepted guidelines.⁷

The distribution of subjects across dose levels was generally similar. However, there were somewhat higher percentages of eslicarbazepine subjects that needed up-titration to dose Level B or C, respectively, compared to carbamazepine-CR. The majority of subjects remained at dose Level A (eslicarbazepine: 271/401 (67.6%), carbamazepine-CR: 317/412 (76.9%)). As a consequence, the number of subjects at dose Level B (eslicarbazepine: 70/401 (17.5%), carbamazepine-CR: 61/412 (14.8%)) and Level C (eslicarbazepine: 60/401 subjects (15.0%), carbamazepine-CR: 34/412 (8.3%)) as last evaluated dose was limited. Moreover, the ages of patients achieving dose Level C were skewed towards younger subjects although the ages between groups were roughly comparable. There was also higher percentage of eslicarbazepine subjects using concomitant AEDs (25.7%) compared to carbamazepine-CR subjects (18.0%) during the evaluation and down-titration periods. To understand a possible impact of this imbalance on the study outcome, a sensitivity analysis was conducted in which patients with concomitant AEDs were regarded non-responders. The sensitivity analysis yielded similar results as the original analysis.

For the primary efficacy endpoint, the proportion of seizure free subjects during the 26 week evaluation period at the last evaluated dose level was slightly lower in the eslicarbazepine arm compared to the carbamazepine-CR group (276/388 (71.1%) versus 300/397 (75.6%), per-protocol;⁸ set). The average risk difference (ARD) was -4.28 (95% CI: -10.3, 1.74) and non-inferiority of eslicarbazepine with carbamazepine-CR was concluded based on the pre-specified non-inferiority margin of an absolute difference of -12%, as the one-sided 97.5% CI was greater than -12%. The results from the analysis on the full analysis set (FAS) as well as from the planned sensitivity analyses were largely consistent with the primary analysis, thus showing that the conclusion of non-inferiority did not depend on the method chosen for the primary analysis.

Consistent results were also shown for the analyses of secondary outcomes: seizure-free subjects after one year of treatment (251/388 (64.7%) versus 279/397 (70.3%) seizure-free patients in the eslicarbazepine and in the carbamazepine-CR group, respectively; ARD: -5.46%, 95% CI: -11.88, 0.97) as well as for the relative risk difference during the evaluation period and during one year of treatment.

Both results, however, were close to the -12% margin. Another notable observation is the numerically smaller effect size for eslicarbazepine compared to carbamazepine-CR such that the probability for treatment failure at the end of the evaluation period was nearly twice as high for patients receiving eslicarbazepine compared to carbamazepine-CR (12% versus 6%).

Moreover, due to the study design, Study 311 did not allow for assessment of a dose response relationship. Further, in Studies 045, 046 differences in dose response for 1200 mg/day versus 1600 mg/day did not reach significance providing no efficacy

⁷ European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), 22 July 2010. Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders (CPMP/EWP/566/98 Rev. 2/Corr).

⁸ The **per-protocol (PP)** analysis is restricted to the participants who strictly adhered to the protocol. Also known as 'on-treatment' analysis.

support for the use of 1600 mg/day in this context. Therefore, the safety and tolerability of 1600 mg/day dose must be acceptable to be recommended.

Paediatric indication

Data from three clinical trials have been submitted to support efficacy of eslicarbazepine in the add-on treatment of POS in children. The main support was derived from two pivotal studies, the Phase III Study 305 and the Phase II Study 208. Both studies were double blind and placebo-controlled with a minimum duration of the maintenance period of eight weeks (Study 208) and 12 weeks (Study 305), respectively. Eslicarbazepine was tested at doses of 20 and 30 mg/kg/day, up to a maximum of 1,200 mg/day. Whereas in Study 208 the targeted dose was 30 mg/kg/day, the initial target dose in Study 305 was 20 mg/kg/day, which could be further titrated to 30 mg/kg/day only during the titration period.

It was the opinion of the European regulatory authorities that the results of efficacy trials performed in adults with refractory partial epilepsies, could to some extent be extrapolated to children provided the dose is established. For eslicarbazepine, efficacy for the add-on treatment of adults with POS with or without secondary generalisation has been well characterised in the three pivotal studies (Studies 301, 302 and 303).

Study 202 was an uncontrolled, open label PK study and efficacy data from this study can be considered only supportive. The study recruited 10 patients each in one of three age groups and showed a dose-dependent decrease in relative (%) seizure frequency in age Group 1 (2 to 6 years) and Group 3 (12 to 17 years), but not in Group 2 (7 to 11 years). Finally, the sponsor has presented long term efficacy data from open label follow-up studies of Study 305 and Study 208. The data suggested that efficacy was either maintained or improved over time. However, the open label design and the high drop-out rates, prevent robust conclusions being drawn from these data.

The clinical evaluator agrees with the Committee for Medicinal Products for Human Use (CHMP)'s position that while efficacy of the 20 mg/kg/day dose has not been convincingly established, population PK simulations have shown comparable exposure to eslicarbazepine at a dose of 20 mg/kg/day in children older than six years and at 800 mg/day in adults. The same applies to the paediatric dose of 30 mg/kg/day and the adult dose of 1200 mg/day. Both 800 mg/day and 1200 mg/day doses have previously been shown to be effective doses in adults and are currently approved for use in add-on therapy of POS. Based on the comparative exposure findings and given that disease expression of partial epilepsies is similar in adults, adolescents and children, the evaluator agrees that an extrapolation of the established efficacy of eslicarbazepine in adults to children down to seven years of age was possible at the proposed maintenance dose range.

Safety

Safety in adult population

The known safety profile of eslicarbazepine was largely based on the data from placebo-controlled Phase II and III clinical trials with eslicarbazepine as adjunctive therapy in adult epileptic subjects supporting the initial marketing authorisation application (Studies 201, 301, 302, and 303). A subsequent Phase III Study 304 supplemented the original safety database with the respective open label extension studies. The adjunctive studies used doses up to 1200 mg/day. Subsequently, the pivotal monotherapy Study 311, and data from two pooled conversion to monotherapy Studies 045 and 046 provided further safety data. In all three monotherapy studies, patients could receive eslicarbazepine up to a maximum daily dose of 1600 mg. However, no integrated analysis of the monotherapy safety data was performed due to differences in study design of the pivotal and supportive studies.

In these studies, a dose-dependent increase in treatment-emergent adverse events (TEAE) was observed for several possibly related TEAEs and TEAEs leading to discontinuation of study medication. TEAEs leading to discontinuation were reported in 8.7%, 11.6%, and 19.3% of the patients receiving 400 mg, 800 mg, and 1200 mg eslicarbazepine, respectively, based on an integrated safety data analysis. In the subsequent Study 304 (Part 1) discontinuations due to TEAEs were reported for 12% and 25.7% of subjects with doses of 800 mg and 1200 mg eslicarbazepine.

The most common TEAEs in the placebo-controlled trials in adult epileptic subjects treated with eslicarbazepine as add-on therapy for partial seizures were dizziness, somnolence (very common, in $\geq 1/10$ patients), headache and nausea (common, in $\geq 1/100$ to $< 1/10$ patients). There were no changes in laboratory parameters that indicated a safety concern and there were also no clinically relevant changes in vital signs, body weight or body mass index (BMI) during the studies. On the review of the monotherapy study data, the safety of eslicarbazepine was largely consistent with the known safety profile in the adjuvant treatment setting. The most common adverse reactions with eslicarbazepine as add-on treatment for POS are dose-related and belong to the System Organ Classes (SOCs) nervous system disorders and gastrointestinal disorders including dizziness, somnolence, headache and nausea. The most common TEAEs reported for eslicarbazepine in POS monotherapy were in line with those already identified for the adjunctive setting.

In the Study 311, most notably, since the study design of the pivotal Study 311 allowed up-titration according to seizure severity, subjects were not evenly distributed between dose groups. Subsequently, 15% of the subjects (60 out of 401 patients in the eslicarbazepine group) received 1600 mg/day in dose Group C, whereas all other subjects received eslicarbazepine doses up to 1200mg/day (dose Groups A or B), for which safety had already been established in the add-on setting. In the evaluator's opinion, this low number of patients prevents adequate safety assessment of the proposed maximum dose in the monotherapy setting of 1600 mg and further understanding of the possible dose relationship of TEAEs.

Moreover, analysis of the baseline demographic characteristics of the last achieved dosing levels in Study 311 suggested that there was an age gradient, such that patients aged > 49 comprised just 10% of dose Level C subjects (1600 mg/day) versus 17.1% dose Level B (1200 mg/day) and 28.8% of dose Level A subjects (800 mg/day). So very little data is provided in Study 311 to support safety of the 1600 mg dose in the age > 49 .

TEAEs in the supportive conversion to monotherapy study pool (Studies 045 and 046) were reported with a higher incidence in the 1600 mg dose group compared to the 1200 mg dose group (81.4% versus 73.2%). Furthermore, discontinuation due to TEAEs was almost twice as high in the 1600 mg dose group compared to the 1200 mg dose group (15.3% versus 8.1%) and hyponatraemia was reported to be serious in 1.2% of subjects on 1600 mg in the supportive conversion-to-monotherapy study pool compared to no such event in the 1200 mg dose group.

In the general population, the prevalence of hyponatremia increases with age and may be more common in women. It is linked to falls, higher systolic blood pressure, increased rates of hospitalisation and higher risk of in hospital mortality. The clinical safety analysis, while highlighting episodes of hyponatremia.

The clinical evaluator looked at other studies involving 1600 mg/day dosing (Studies 307 and 308). It is noted that there has been no pooled analysis provided by the sponsor of subjects receiving 1600 mg/day specifically addressing safety of this dose. In the evaluator's opinion, an integrated analysis of hyponatremia by age would be possible for this dose with the data available. However, from Studies 307 and 308, the overall impression of the evaluator is that the special interest TEAE of hyponatraemia could be

considered very common (> 1/10) in subjects over the age of 49 treated with eslicarbazepine 1600 mg/day. In the opinion of the evaluator, at least the PI should be amended to express significant caution in patients > 49 years.

Moreover, it should be noted that eslicarbazepine is a third generation dibenz[b,f]azepine AED and is closely related to oxcarbazepine. Following oral administration of both active substances, the same active moieties (eslicarbazepine, R-licarbazepine and oxcarbazepine) are found in plasma, though in different proportions. Therefore, class related adverse reactions which have been reported with oxcarbazepine including rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (such as Stevens-Johnson syndrome), systemic lupus erythematosus or serious cardiac arrhythmias, while not observed during the eslicarbazepine epilepsy clinical development program, cannot be excluded with eslicarbazepine use.

Paediatric safety

The main basis for the safety assessment in support of the paediatric indication was an integrated analysis of the key Phase II/III paediatric Studies 208 and 305. Overall, the evaluator agrees that the data are robust enough to be assured on the safety profile of eslicarbazepine when used in children aged more than six years with refractory partial epilepsy.

No age or dose specific safety concern was identified based on the available data that would have emerged as a new issue with the use of eslicarbazepine. In most aspects, the safety profile of eslicarbazepine in the paediatric population resembled the one in adults. Similar to the findings in adult studies, a dose-dependent trend in the incidence of possibly related TEAEs was observed and the most commonly reported related TEAEs were somnolence, ataxia, vomiting, dizziness and diplopia.

When compared to adults, a higher incidence of serious adverse events has been reported in the paediatric studies, mainly consisting of convulsions. However, overall, serious TEAEs occurred at a low incidence, without specific pattern in single subjects only and in accordance with the known safety profile of eslicarbazepine. The number of deaths (three) reported from the eslicarbazepine paediatric studies was not higher as compared to other studies conducted in patients with epilepsy. It was furthermore considered unlikely that the cases deaths were related to study medication.

Treatment-emergent adverse events that occurred more frequently in paediatric patients compared to adults were: convulsions, pyrexia and infections and infestations. However, within the paediatric studies, these events occurred at similar (pyrexia) or lower (convulsions as well as infections and infestations) rate in the placebo group compared to eslicarbazepine. It is likely that this adverse event (AE) related to the underlying disease rather than eslicarbazepine. Infections occur usually rather frequent in (smaller) children and thus a higher reporting rate compared to adults is not surprising and may not be attributed to eslicarbazepine.

Treatment-emergent adverse events leading to discontinuation were higher in the paediatric eslicarbazepine group than for placebo and also for paediatric patients versus adults. However, when comparing this finding to other studies with AEDs, it is the evaluator's opinion that the rates are fairly comparable.

Two events of dermatitis allergic (0.8%) were reported in paediatric patients receiving eslicarbazepine (compared to none in the placebo group). This event was not reported in adults, although skin reactions are known to occur under treatment with eslicarbazepine. Dermatitis allergic is included as an uncommon safety concern in the PI.

With regards to laboratory findings, the incidences of cases of increased gamma glutamyltransferase (GGT) and decreased thyroxine (T₄) were higher in the paediatric group when compared to adults. Neither appeared to be clinically significant.

Hypothyroidism and liver disorders are already included in the PI as adverse reactions. No further changes to the safety information are considered necessary.

While the effects of eslicarbazepine on cognition have been evaluated in Study 208 for up to four years, suggesting that eslicarbazepine has no negative consequences for attention. On the basis of the available data, is unlikely that eslicarbazepine would have long term effects on brain development, learning and intelligence.

Eslicarbazepine was generally well-tolerated when used as adjuvant therapy in the treatment of children with POS. The incidence of serious adverse events and discontinuations due to AEs was overall low although slightly higher in paediatric subjects compared to adults. There were no new major safety concerns arising from the paediatric clinical studies at the applied maintenance doses of 20 and 30 mg/kg/day. The safety profile of eslicarbazepine in children older than six years was overall consistent with the known safety profile of eslicarbazepine in adults.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 22.0; (dated 2 March 2017; data lock point (DLP) 21 October 2015) and Australian-specific annex (ASA) version 1.0 (dated 22 April 2020) in support of this application. With response to a TGA request for information, the sponsor submitted ASA version 2.0 (dated 07 December 2020) aligned to EU-RMP version 22.0 (dated 2 March 2017; DLP 21 October 2015).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.⁹

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hyponatremia	Ü	–	Ü	–
	Cutaneous adverse reactions	Ü*	–	Ü	–
Important potential risks	Thyroid function changes	Ü	–	Ü	–
	International normalised ratio (INR) and activated partial thromboplastin time (aPTT) increase	Ü	–	Ü	–
	Cardiovascular/cerebrovascular ischemia	Ü*	–	Ü	–

⁹ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
	Potential for suicidality as antiepileptic drug	Ü	-	Ü	-
	Bone disorders	Ü	-	Ü	-
Missing information	Exposure during pregnancy	Ü	Ü†	Ü	-
	Paediatric population (< 2 years of age)	Ü	-	Ü	-
	Elderly population	Ü	-	Ü	-
	Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	Ü	-	Ü	-

* Targeted follow-up questionnaires

† International European Registry of Antiepileptic Drugs and Pregnancy (EURAP)

- The summary of safety concerns is considered acceptable from an RMP perspective.
- The sponsor has proposed routine pharmacovigilance activities for all safety concerns including targeted follow-up forms for cutaneous adverse reactions and cardiovascular/cerebrovascular ischemia. An additional pharmacovigilance activity, in the form of an observational pregnancy registry in Europe, is considered relevant to Australia.
- The sponsor has proposed routine risk minimisation activities through the PI and Consumer Medicines Information (CMI) to address all important potential and identified risks. The sponsor has not proposed any additional risk minimisation activities. The proposed risk minimisation plan is considered acceptable.

Risk-benefit analysis

Delegate's considerations

Eslicarbazepine acetate (Zebinix) has established efficacy as a monotherapy treatment in adult patients with partial onset seizure and as an adjunctive therapy in adults, adolescents and children aged above six years, with POS.

Seizure frequency per four week period was consistently statistically significantly lower in the active groups compared with placebo (for example, least squares (LS) mean difference versus placebo in Studies 301 to 304 between -1.4 to -2.7 eslicarbazepine 800 mg and between -1.9 to -2.8, eslicarbazepine 1200 mg/day. Only one comparison in Study 304 was not statistically significant (LS mean 6.5 for eslicarbazepine 800 mg and LS mean 6.0 for placebo; P-value = 0.058). Approximately 30% to 40% of patients demonstrated a $\geq 50\%$ reduction in seizures and all findings were statistically significant compared with placebo, except in two instances when eslicarbazepine 800 mg was compared with placebo in Studies 303 and 304. Numbers needed to treat for the $\geq 50\%$ reduction in seizures

outcome were eight with eslicarbazepine 800 mg, and ranged from five to seven with eslicarbazepine 1,200 mg. There were relatively few discontinuations in the long term studies in the group on the maximum of 1200 mg/day.

Due to the very close pharmacological relationship of eslicarbazepine with oxcarbazepine it is highly probable, that AEs, which occur after administration of oxcarbazepine may also occur after administration of Zebinix.

Eslicarbazepine was generally well-tolerated with particular reference to potential cognitive effects when used as adjuvant therapy in the treatment of children with POS. The incidence of serious adverse events and discontinuations due to AEs was overall low although slightly higher in paediatric subjects compared to adults. However, many of the serious adverse events and discontinuations were due to intrinsic factors or epilepsy and unrelated to eslicarbazepine.

There were no additional safety concerns arising from the paediatric clinical studies at the applied maintenance doses of 20 and 30 mg/kg/day. The safety profile of eslicarbazepine in children older than six years was overall consistent with the known safety profile of eslicarbazepine in adults.

Overall the benefit-risk balance of Zebinix (eslicarbazepine acetate) as a monotherapy treatment in adult patients with partial onset seizure and as an adjunctive therapy in adults, adolescents and children aged above six years, with POS is considered positive.

Proposed action

Overall Zebinix is approvable as the quality, nonclinical and clinical evaluators have all recommended approval. The delegate considers that sufficient data and justification have been provided to support the registration of Zebinix on quality, safety and efficacy grounds for the treatment of partial onset seizures.

Advisory Committee considerations¹⁰

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Zebinix (eslicarbazepine acetate) 200 mg and 800 mg, tablet, blister pack, indicated for:

Zebinix is indicated as:

- *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.*

¹⁰ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

- Zebinix (eslicarbazepine acetate) is to be included in the Black Triangle Scheme. The PI and CMI for Zebinix must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Zebinix EU-RMP (version 22.0, dated 2 March 2017, DLP 21 October 2015), with ASA (version 2.0, dated 7 December 2020), included with submission PM-2020-01850-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Zebinix approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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