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Committee for Medicinal Products for Human Use (CHMP)

Zebinix

(Eslicarbazepine acetate)

Procedure No. EMEA/H/C/000988/P46/023

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

On 9th April 2014, the MAH submitted a completed paediatric study for eslicarbazepine acetate (BIA-2093-305), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study BIA-2093-305 is part of the paediatric investigation plan (PIP) for eslicarbazepine acetate (P/0197/2013 issued on 2 September 2013).

A short critical expert overview has also been provided.

Scientific discussion

Information on the pharmaceutical formulation used in the study(ies)

Study treatments were provided as an oral suspension (50 mg/mL) for use in the age group of 2–6 years (stratum I) or as white oblong tablets (200 mg) for use in the older children and adolescents (≥7 years of age; strata II and III).

Clinical aspects

Study BIA-2093-305, title "Efficacy and safety of eslicarbazepine acetate (BIA 2-093) as adjunctive therapy for refractory partial seizures in children: a double-blind, randomised, placebo-controlled, parallel-group, multicentre clinical trial"

Description

This was a phase III, double-blind, randomised, placebo controlled, multicentre, parallel group (part I) trial to evaluate efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in children aged 2 to less than 18 years with a diagnosis of partial onset seizures that were refractory to treatment with 1 to 2 anti-epileptic drugs (AEDs) with 4 subsequent one year open-label extension phases (part II-V).

Study BIA-2093-305 has a date of completion of September 2015 as per agreed PIP (EMEA-00069-PIP02-M04). The first patient was enrolled by 07 December 2007 and the date of last patients completing the first open-label extension period (part II) was 22 October 2013.

The MAH has thus reported procedures and results to parts I and II of the study in the current submission. In the study report covering part I and II of the study it is stated, that separate study reports will be written for parts III-IV of the study.

Methods

- **Objective(s)**

The primary objective of the study was to assess the efficacy of ESL as an adjunctive therapy in children and adolescents with refractory partial seizures.

The secondary objectives of the study were to assess:

- The safety and tolerability of ESL as an adjunctive therapy in children and adolescents with refractory
- partial seizures.
- The proportion of seizure-free patients and of patients with more than 75% reduction in seizure

- frequency.
- The frequency of patients with exacerbations.
- The duration of seizures and severity of seizures (using the Hague seizure severity scale).
- The potential for rebound effects and withdrawal phenomena.
- The potential for interactions between ESL and concomitant antiepileptic drugs (AEDs).
- The seizure frequency by seizure type.
- The maintenance of the therapeutic effect of ESL during long-term treatment in Part II, Part III, Part IV, and Part V of the study.

- **Study design / Treatments**

A phase III, randomised, double blind, placebo-controlled, multinational parallel-group (part I) study with 4 subsequent long-term, open-label extension periods (parts II-V).

Part I consisted of the following treatment periods:

- An 8-week observational baseline period:

Patients entered the baseline period after the screening visit (Visit 1). At the end of the baseline period (Visit 2), eligible patients were randomised in a 1:1 ratio (stratified by age: stratum I: 2-6 years; stratum II: 7-11 years; stratum III: 12-18 years) to receive ESL or placebo in addition to concomitant therapy with 1 or 2 AEDs.

- A 6-week double-blind titration period:

The recommended dose ("target dose") of double-blind study treatment was 20 mg/kg/day (up to a maximum of 1200 mg/day).

- A 12-week double-blind maintenance period:

After the titration period, patients entered the 12-week maintenance period (from Visit 4 to 7).

Patients received a maximum dose of 30mg/kg/day (maximum of 1200 mg/day).
Up-titration was not permitted during the maintenance period; down-titration was allowed only once.

- An up to 4-week double-blind tapering-off period:

Study treatment was tapered off in 10 mg/kg/day steps or in the same doses given during the titration period (as applicable) every 2 weeks.

- A 4-week observational follow-up period.

Part II of the study consisted of the following:

- A 48-week open-label extension period:

The starting ESL dose was 10 mg/kg/day (maximum 800 mg/day).
The dose was titrated according to clinical response in the dose range from 10 mg/kg/day to 30 mg/kg/day (or 800 mg/day to a maximum of 1200 mg/day). Down-titration was allowed.

- **Study population / Sample size**

Main criteria for inclusion:

- Diagnosis of epilepsy for at least 6 months prior to enrolment; for patients from the Czech Republic: diagnosis of epilepsy for at least 24 months prior to enrolment (Amendment 1 Czech Republic, 05 Oct 2007).

- Children 2 to 16 years of age; as per Global Amendment 4 (16 Sep 2010): children 2 to 18 years of age; for patients from Romania: children 2 to 17 years of age (Amendment 1 Romania, 09 Nov 2010).

- At least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 1 or 2 AEDs; for patients from the Czech Republic: at least 4 partial-onset seizures in the last month prior to enrolment despite stable therapy with adequate dosage of 2 AEDs (Amendment 1 Czech Republic, 05 Oct 2007).

- At least 4 partial-onset seizures during each 4-week interval of the 8-week baseline period.

- Stable dose regimen of AEDs during the 8-week baseline period.

- Current treatment with 1 or 2 AEDs (any AED except oxcarbazepine); if present, vagus nerve stimulation is considered an AED (this last addition was introduced per Global Amendment 1 [20 Dec 2007]).

Patients with primarily generalised seizures, known progressive neurological disorders, known second or third degree atrioventricular block (introduced per Global Amendment 4 [16 Sep 2010]), history of status epilepticus within the 3 months prior to enrolment, seizures of non-epileptic origin, Lennox-Gastaut syndrome or West syndrome were excluded from the study.

Planned: 252 patients (126 per treatment group).
Treated: 304 patients (155 with ESL, 149 with placebo).

Analysed for efficacy:
Part I: 263 in intention-to-treat (ITT) set (134 ESL, 129 placebo) (excluding stratum I before investigational medicinal product [IMP] recall); 198 in per protocol set (97 ESL, 101 placebo); 41 in stratum I before IMP recall (21 ESL, 20 placebo).

Part II: 225 ESL in the ITT set.

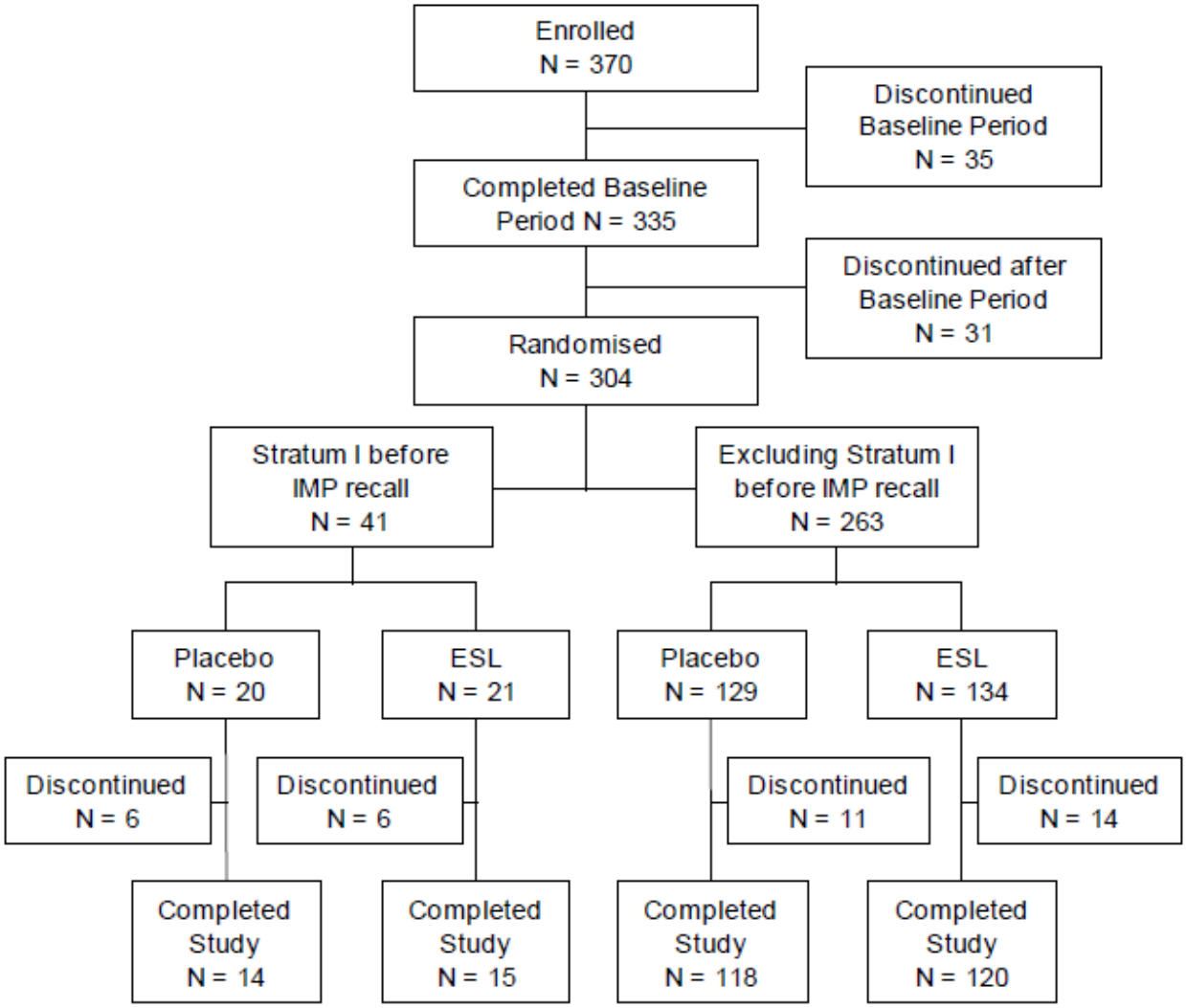
Analysed for safety:
Part I: 263 in the safety set (134 ESL, 129 placebo) (excluding stratum I before IMP recall); 41 in stratum I before IMP recall (21 ESL, 20 placebo).

Part II: 260 ESL in the combined safety set (i.e. all treated patients).

In the safety set, 37 patients (27.6%) in the ESL group and 28 patients (21.7%) in the placebo group had a major protocol violation or a treatment duration in the maintenance period of <11 weeks. These patients were therefore excluded from the PP set, which consequently included 97 patients (72.4% of the safety set) in the ESL group and 101 (78.3%) in the placebo group.

The CHMP noted that the percentage of patients with major protocol violations in both treatment groups appears rather high, this finding was more pronounced in the active treatment group.

Study disposition flow chart of study 305, part I:



On 04 Jun 2009, the distribution of oral suspension of study medication was stopped due to stability issues resulting in dark spots visible in the vials. Patients in stratum I (2-6 years of age) who received IMP as oral suspension had to stop intake immediately and any unused study medication had to be returned. On 19 Jun 2009 it was decided to recall all oral suspension study medication. The investigators were informed on 22 Jun 2009 that patients had to perform their EDVs and follow-up visits. Affected patients were excluded from primary efficacy analyses. Stratum I patients (2-6 years of age) were offered to switch to the tablet formulation if parents and investigators were of the opinion that the patient could swallow tablets.

The CHMP noted that after closure of the part I database and unblinding, it was found that the issue with the oral suspension only affected the placebo formulation and thus no impact on efficacy was concluded in the study report. Nevertheless, affected patients had been excluded form the primary efficacy analyses.

- Outcomes/endpoints

Part I of the study

Two primary efficacy variables were defined:

1. Responder rate, defined as the proportion of patients with at least a 50% decrease in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

2. Relative reduction in the standardised 4-week seizure frequency from the baseline period to the 12-week maintenance period.

The **secondary efficacy variables** were:

- Standardised seizure frequency per period of the baseline, titration, maintenance, and tapering-off periods.
- Relative change in seizure frequency from the baseline period to the 12-week maintenance period (≥25%; >–50% to <25%; ≥–75% to ≤–50%; <–75%).
- Proportion of patients who are seizure-free during the maintenance period.
- Standardised seizure frequency by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other) during the maintenance period. Seizures with missing seizure type information were considered as unclassified for the analysis.
- Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, ≥5 min, unknown.
- Seizure severity assessed with the 13-item Hague seizure severity scale.
- Number of days with seizures (standardised to 4-week time period).
- Treatment retention time, defined as the time to first occurrence of one of the following during the titration or maintenance period: withdrawal of study medication due to AEs or withdrawal of study medication due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
- Seizure exacerbations during tapering-off or follow-up period.

Part II of the study

- Standardised seizure frequency per 4-/12-week interval (weeks 1-4, 5-16, 17-28, 29-40, ≥41).
- Absolute and relative change from Part I baseline in seizure frequency per 4-/12-week interval.
- Responder rate per 4-/12-week interval: responders were defined as those patients with a relative seizure reduction of at least 50% in the respective time interval compared to Part I baseline.
- Categorised relative change in seizure frequency per 4-/12-week interval: relative change in seizure frequency from the Part I baseline period to each 4-/12-week interval (≥25%; >–50% to <25%; ≥-75% to ≤–50%; <–75%).
- Exacerbations in seizure frequency (increase in relative change in seizure frequency of ≥25%) per 4-/12-week interval compared to the Part I baseline and maintenance periods.
- Seizure free patients per 4-/12-week interval.
- Standardised seizure frequency per 4-/12-week interval by seizure type (simple partial, complex partial, partial evolving to secondary generalised, unclassified, other): seizures with missing seizure type information were considered as unclassified for analysis.
- Standardised number of days with seizures per 4-/12-week interval.

- Seizure duration (as classified in the diary): <30sec, ≥30 sec - <1 min, ≥1 min - <5 min, and ≥5 min.
- Treatment retention time, defined as the time to first occurrence of withdrawal of study medication due to AEs or due to lack of efficacy (defined as seizure exacerbation ≥100% compared to the baseline period).
- Seizure severity (Hague seizure severity scale).

In both study parts, **safety** was assessed on the basis of the following observations and measurements:

- Reports of adverse events (AEs), including serious adverse events (SAEs).
- Safety laboratory (haematology, biochemistry, and urinalysis).
- Vital signs.
- 12-lead electrocardiogram (ECG) parameters.
- Physical and neurological examinations.
- Sexual maturation assessment.

- **Statistical Methods**

The sample size calculation was based on the 2 primary efficacy variables. At least 100 patients treated with ESL were to be followed-up for at least 1 year and included in safety analyses. Both primary variables were intended to be sufficiently powered with at least 80% power to show a significant difference following a hierarchical testing procedure at a 2-sided significance level of 0.05.

Efficacy analysis:
Primary (applicable to Part I only):
The responder rate was analysed by a Cochran-Mantel-Haenszel (CMH) test with stratum group (I: 2-6 years; II: 7-11 years; III: 12-16 [18] years) as the stratification factor.
The relative reduction in standardised seizure frequency was compared between treatment groups using an analysis of covariance (ANCOVA) that modelled the relative change in standardised seizure frequency as a function of stratum group (I: 2-6 years; II: 7-11 years; III: 12-16 [18] years), baseline seizure frequency, and treatment.
The second primary null hypothesis (no treatment difference with regard to the relative reduction in standardised seizure frequency) was only tested if the first primary null hypothesis (no treatment difference with regard to response rates) had been rejected following the hierarchical testing strategy, which controlled for type I error inflation due to multiple testing. Tests were performed 2-sided at a significance level of 0.05.

Secondary and Part II efficacy variables:
Secondary efficacy variables and efficacy variables for Part II of the study were analysed descriptively.

Results

- **Recruitment/ Number analysed**

Please refer to study population/sample size, above.

- **Baseline data**

The median standardised number of seizures during the baseline period was lower in the ESL group (11.5; range: 3.7, 605.8) than in the placebo group (17.0; range: 3.9, 1972.5).

Table 8 – Standardised seizure frequency during the baseline period (safety set)

Parameter	Placebo (N=129)			ESL (N=134)		
	n (%)	Mean (SD)	Median (range)	n (%)	Mean (SD)	Median (range)
Any seizure	129 (100)	62.0 (186.19)	17.0 (3.9, 1972.5)	134 (100)	36.6 (72.47)	11.5 (3.7, 605.8)
Simple partial	71 (55.0)	66.0 (198.42)	14.0 (0.5, 1564.5)	65 (48.5)	34.3 (82.38)	8.0 (0.4, 605.8)
Complex partial	78 (60.5)	25.3 (53.94)	6.2 (0.5, 405.0)	84 (62.7)	19.3 (40.06)	6.0 (0.4, 233.0)
Partial evolving to secondarily generalised	63 (48.8)	14.8 (26.86)	6.0 (0.5, 150.0)	60 (44.8)	12.6 (31.19)	4.0 (0.4, 193.0)
Unclassified	18 (14.0)	4.1 (4.15)	2.6 (0.4, 13.8)	17 (12.7)	10.3 (23.93)	0.9 (0.5, 99.4)
Other	10 (7.8)	32.7 (51.11)	3.7 (0.5, 141.5)	11 (8.2)	11.8 (19.00)	4.9 (0.5, 62.5)

Table 11 – Concomitant antiepileptic drugs during the study (safety set)

	Number (%) of patients	
AED	Placebo (N=129)	ESL (N=134)
Patients with at least 1 concomitant AED	129 (100.0)	134 (100.0)
Total number of AEDs given concomitant at the end of the baseline period		
1	25 (19.4)	21 (15.7)
2	94 (72.9)	98 (73.1)
3	10 (7.8)	15 (11.2)
AEDs used a		

- **Efficacy results**

Part I

For both **primary efficacy variables**, the response rate and the relative change in the standardised seizure frequency during the maintenance period, no statistically significant difference between ESL and placebo was found. Forty-one patients (30.6%) in the ESL group compared to 40 patients (31.0%) in the placebo group were responders, resulting in a non-significant odds ratio of 0.97 (95% confidence interval [CI]: 0.57, 1.63; p=0.9017). The least square (LS) mean relative change in the standardised seizure frequency was higher in the ESL group (-18.1%) than in the placebo group (-8.6%), resulting in a LS mean difference of 9.5% (95% CI: -6.71, 25.77; p=0.2490).

Responder rates and corresponding between-treatment differences were identical or similar to those in the primary analysis described above when using the randomised set (identical to the ITT set; the mITT set, or the PP set (97 ESL patients, 101 placebo patients).

Secondary efficacy findings were as follows:

- Frequency of seizure-free patients: maintenance period: 3.9% ESL, 2.4% placebo; tapering-off period: 9.2% ESL, 12.6% placebo.
- Frequency of patients with seizure reduction of at least 75%: maintenance period: 15.6% ESL, 12.9% placebo; tapering-off period: 13.4% ESL, 20.3% placebo.
- Frequency of patients with exacerbation (increase of ≥25%): maintenance period: 13.3% ESL, 13.7% placebo; tapering-off period: 14.3% ESL, 15.3% placebo.

- Seizure duration: The majority (>80%) of seizures during the maintenance period lasted <1 minute in both treatment groups.

- Seizure severity: During the study, small mean increases in the total score of the Hague seizure severity scale were seen in both treatment groups, slightly larger in the ESL group (mean increases between 1.4 and 2.5) than in the placebo group (mean increases between 0.5 and 1.6).

- Number of days with seizures: In each study period, the mean standardised number of days with seizures was slightly lower in the ESL group than in the placebo group. In both treatment groups, the mean standardised number of days with seizures was highest during the baseline period (12.2 days ESL; 13.9 days placebo) and lowest during the maintenance period (9.3 days ESL; 11.9 days placebo).

- There was no interaction between the number of concomitant AEDs or concomitant carbamazepine and treatment in the ANCOVA of the relative change in standardised seizure frequency.

- No rebound effects were observed. The standardised seizure frequency during tapering-off and follow-up periods increased in relation to maintenance period, but not to a value greater than that observed at baseline. Furthermore, the increase in standardised seizure frequency during tapering-off and follow-up periods in relation to baseline was similar in both treatment groups.

- Efficacy results showed a trend in favour of ESL compared to placebo when the standardised seizure frequency is based on the titration + maintenance period instead of the maintenance period, and also when the ITT (Intended to treat) set is restricted to patients from strata II and III. However, between-treatment differences were not statistically significant.

- A statistically significant difference in favour of ESL compared to placebo was observed in an analysis of the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III (difference 16.2%; p=0.0359).

The CHMP noted that in part I of study 305 no superior efficacy of ESL over placebo could be shown as adjunctive treatment in children with refractory partial onset seizures. The only statistically significant difference in favour of ESL compared to placebo (in an analysis of the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III) resulted from a post-hoc analysis.

Part II

Efficacy findings in Part II per variable in the total ITT set were as follows:

- The total responder rate during Part II was 46.7%. Responder rates steadily increased during Part II, from 44.9% during weeks 1-4 to 57.5% during weeks >40.

- The total median standardised seizure frequency during Part II was 6.1, resulting in a median relative change compared to the baseline period of -46.7%. The median relative change was larger in the previous placebo group (-51.4%) than in the previous ESL group (-40.4%). The total median standardised seizure frequency decreased from 7.0 during weeks 1-4 to 4.0 during weeks >40.

- Five patients (2.2%) were seizure-free during Part II. The proportion of seizure-free patients was 8.9% during weeks 1-4, 6.7% during weeks 5-16, 13.8% during weeks 17-28, and 14.2% during weeks 29-40.

- The proportion of patients with exacerbation compared to the baseline period was 14.2%. Respective proportions decreased during Part II, in particular during the first half (from 19.6% during weeks 1-4 to 8.2% during weeks 17-28). The total proportion of patients with a seizure reduction of at least 50% compared to the baseline period was 46.6%; it was 44.9% during the first interval, 48.0% during the second interval and at least 54.8% during each of the subsequent intervals.
- Seizure severity: small mean increases in the total score of the Hague seizure severity scale were seen during Part II.
- The median standardised number of days with seizures was 4.8 days overall; it continuously decreased over the course of Part II, from 5.0 days during the first to 2.9 days during the last time interval.

Of the 260 patients enrolled into Part II, 183 (70.4%) completed Part II and 152 (58.5%) chose to continue treatment in Part III of study 305.

The CHMP noted that, taking into consideration the open-label character and the drop-out rate of approximately 30% of part II together with the results of part I of study 305, no robust conclusions of efficacy of ELS in the evaluated population can be drawn from the this study part (II) of study 305.

- **Safety results**

Part I

The safety results did not reveal any new findings of concern, compared to prior studies. The main safety results were as follows:

- A total of 112 patients (83.6%) in the ESL group compared to 94 (72.9%) in the placebo group experienced at least 1 TEAE (Treatment-Emergent Adverse Event). Most frequently reported TEAEs (>5% of patients in any treatment group) were headache (18 patients [13.4%] ESL, 8 patients [6.2%] placebo), nasopharyngitis (15 [11.2%] ESL, 15 [11.6%] placebo), somnolence (15 [11.2%] ESL, 6 [4.7%] placebo), convulsion (13 [9.7%] ESL, 14 [10.9%] placebo), pyrexia (10 [7.5%] ESL, 7 [5.4%] placebo), pharyngitis (9 [6.7%] ESL, 9 [7.0%] placebo), vomiting (8 [6.0%] ESL, 8 [6.2%] placebo), diplopia (8 [6.0%] ESL, 2 [1.6%] placebo), respiratory tract infection (7 [5.2%] ESL, 7 [5.4%] placebo), nausea (7 [5.2%] ESL, 1 [0.8%] placebo), bronchitis (5 [3.7%] ESL, 7 [5.4%] placebo), and rhinitis (4 [3.0%] ESL, 7 [5.4%] placebo). A higher number of patients treated with ESL compared to placebo (>2% absolute difference) reported headache, somnolence, pyrexia, diplopia, nausea, decreased appetite, vertigo, agitation, dizziness, increased weight, upper abdominal pain, influenza, and asthma.
- A total of 56 ESL patients (41.8%) compared to 32 placebo patients (24.8%) had at least 1 possibly related TEAE. Most commonly reported possibly related TEAEs (≥5% of patients in the ESL group) were somnolence (12 patients [9.0%] ESL, 5 patients [3.9%] placebo), convulsion (7 [5.2%] ESL, 6 [4.7%] placebo), and diplopia (7 [5.2%] ESL, 2 [1.6%] placebo).
- A total of 15 ESL patients (11.2%) compared to 9 placebo patients (7.0%) had at least 1 serious TEAE. The only serious TEAEs reported by more than 1 patient in any treatment group were status epilepticus (3 patients [2.2%] ESL, 0 placebo), convulsion (2 [1.5%] ESL, 2 [1.6%] placebo), bronchopneumonia (2 [1.5%] ESL, 0 placebo), device malfunction (2 [1.5%] ESL, 0 placebo), and pneumonia (1 [0.7%] ESL, 3 [2.3%] placebo).

The CHMP noted that of the 3 status epilepticus cases in the ESL group, 2 occurred during the tapering-off period and during the follow up period (i.e. after withdrawal of ESL), respectively.

In this context it was considered by the CHMP reassuring, that exacerbation in seizure frequency compared to baseline occurred in a lower percentage in ELS compared to placebo treated patients during titration as well as during maintenance period (≥100% exacerbation during titration period in 2.2% ELS vs. 8.5% placebo treated, during maintenance period in 2.3% ELS vs. 6.5% placebo treated patients; ≥25% exacerbation during titration period in 11.2% ELS vs. 14.7% placebo treated, during maintenance period in 13.3% ELS vs. 13.7% placebo treated patients).

Furthermore, responder rates by seizure type showed slightly higher responder rates in the ESL group compared to the placebo group with respect to partial evolving to secondary generalized seizures, however overall frequencies for these seizure type was generally low.

- A total of 5 patients (3 [2.2%] ESL, 2 [1.6%] placebo) had at least 1 possibly related serious TEAE. These events were vertigo, drug withdrawal syndrome, status epilepticus, and vascular purpura in the ESL group, and irritability, convulsion, and hypotonia in the placebo group.

The CHMP noted that according to the SAE narratives of part I of the study, one further patient had at least 1 possibly related serious TEAE (No. #13506): Exanthema (PT rash) was considered to be probably related to treatment with ESL.

In the case of "vascular purpura" the patient developed a skin rash with "concomitantly spotty-petechial elements fully disappearing with pressing". The rash occurred without subjective complaints (pruritus, burn or pain), without subjective repercussion, and without thrombocytopenia, eosinophilia or pathological liver function tests and was reversible after discontinuation of ESL.

Rash (common) and hypersensitivity (uncommon) are already labeled adverse reactions of Zebinix in the approved adult indication.

The status epilepticus and "withdrawal phenomenon" (PT drug withdrawal syndrome) occurred in a study patient 2 days after final ESL discontinuation in the observational follow-up period.

- Study treatment was discontinued due to a TEAE for 7 patients (5.2%) in the ESL group and 3 (2.3%) in the placebo group. The only TEAE leading to treatment discontinuation reported more than once overall was convulsion (1 patient [0.7%] ESL, 3 [2.3%] placebo).
- Two patients died due to an AE (Adverse Event) during Part I: a 6-year-old female patient treated with **ESL**, due to convulsion, brain oedema, bronchopneumonia, and brain herniation, and a 5-year-old female patient treated with **placebo** due to asphyxia. The events were considered unrelated or unlikely related to study medication.

The CHMP noted that in the death case which occurred in the ESL treatment group, cluster seizures were considered to be the primary event leading to death. The event occurred in a in a 7 year old patient (height 108 cm, weight 20 kg) with a meningomyelocele with hydrocephalus, controlled by a V-P shunt, who had a long standing history of very frequent seizures before study entry (about 60 per months) and who was receiving 3 concomitant AEDs during the study (i.e. vigabatrine, lamotrigine and phenobarbital) allowed as waiver of the respective inclusion criterium. As treatment for the cluster seizures, the patient additionally received 20 mg diazepam rectally.

The event was considered unrelated by the investigator whereas the sponsor concluded that the underlying disease as well as the rather high dose of diazepam (in addition to concomitant phenobarbital) may have contributed to the cluster seizures and subsequent apnoea, respectively

however that it is not possible to completely rule out a contributory role of ESL to the cluster seizures, which is agreed by the assessor.

- During the tapering-off or follow-up period, 16 patients (12.4%) in the ESL group and 10 patients (7.9%) in the placebo group had at least 1 neurological TEAE.
- Changes from a normal laboratory value at baseline to an abnormal value at endpoint occurred in fewer than 25% of patients per laboratory parameter and treatment group and with mostly similar frequency between treatment groups. For any laboratory parameter, no more than 2 patients per treatment group had a laboratory value considered clinically significant by the investigator, with the exception of gamma-glutamyltransferase (GGT) that was clinically significant for 3 patients (2.3%) in the ESL group compared to none in the placebo group. In addition, 4 patients (3.0%) in the ESL group and 1 patient (0.8%) in the placebo group had a decrease from baseline in sodium levels of ≥10 mmol/L. Twelve patients (9.0%) in the ESL group and 3 patients (2.3%) in the placebo group had post-baseline sodium values ≤135 mmol/L (8 patients [6.0%] in the ESL group compared with 3 patients [2.3%] in the placebo group had a sodium value of >130-135 mmol/L).

The CHMP noted that liver disorder was a known adverse drug reaction of Zebinix (uncommon).

A decrease from baseline in sodium levels and low post-baseline sodium values, respectively were found in a higher percentage in active compared to placebo treated patients, however, no ADR of hyponatraemia was reported as ADR in study 305 (part I or part II). Hyponatraemia is already a known AE for Zebinix in the approved adult indication, and as such reflected in the product information.

- No clinically relevant findings were seen in the analysis of vital signs, height, weight, body mass index (BMI), head circumference, sexual maturation assessment, and ECG.
- The safety profile in the subgroup of patients in strata II and III was similar to that seen in the overall safety set.

Part II

Safety results during Part II did not reveal any findings of concern with regard to the long-term safety of ESL in the included population. Frequencies for AE categories were generally similar between groups by previous treatment with the exception of the period of the first 4 weeks of Part II where more patients previously treated with placebo had TEAEs considered at least possibly related. This is also not a finding of concern as the reported TEAEs were central nervous system related (somnolence, diplopia, and ataxia) and it is known that the overall incidence of TEAEs increase with the start of ESL or the increase of ESL doses.

The main safety results during Part II in all patients treated with ESL were as follows:

- 191 patients (73.5%) experienced at least 1 TEAE. Most frequently reported TEAEs were convulsion (39 patients [15.0%]), nasopharyngitis (33 [12.7]), somnolence (24 [9.2%]), vomiting (24 [9.2%]), headache (23 [8.8%]), and pyrexia (22 [8.5%]).
- 86 patients (33.1%) had at least 1 TEAE that was considered at least possibly related to ESL by the investigator. Most commonly reported such TEAEs (≥5% of patients) were somnolence (22 patients [8.5%]) and convulsion (15 [5.8%]).
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- 27 patients (10.4%) had at least 1 serious TEAE; the only serious TEAEs reported by more than 2 patients were convulsion (6 patients [2.3%]) and pneumonia (4 [1.5%]).
- 14 patients (5.4%) had at least 1 TEAE leading to treatment discontinuation; the only such TEAEs reported more than once were convulsion (7 patients [2.7%]), abnormal behaviour (2 [0.8%]), and hypotonia (2 [0.8%]).
- No cases of death were reported during Part II.
- Changes from a normal laboratory value at baseline (OL) to an abnormal value at endpoint occurred in fewer than 30.1% of patients per laboratory parameter. For any laboratory parameter, no more than 3 patients had a laboratory value considered clinically significant by the investigator, with the exception of GGT that was clinically significant for 13 patients (5.8%), and free thyroxine (T4) that was clinically significant for 5 patients (2.2%).
- No clinically relevant findings were seen in the analysis of vital signs, height, weight, BMI, head circumference, sexual maturation assessment, and ECG during Part II.

The CHMP considered that the adverse event profile of study parts I and II was generally consistent with previous data on ESL. No new unique safety concerns occurred within this study. Update or change of product information is therefore not considered necessary at this point.

2. Discussion on clinical aspects

In part I of study 305 no superior efficacy of ESL over placebo could be shown as adjunctive treatment in children with refractory partial onset seizures. The only statistically significant difference in favour of ESL compared to placebo (in an analysis of the relative change in standardised seizure frequency during the titration + maintenance period based on patients in strata II and III) resulted from a post-hoc analysis. These results appear contradictory to the results of study 208, submitted in a previous procedure for Zebinix, in which ESL as adjunctive treatment was statistically significantly different from placebo with respect to the primary efficacy endpoint (improvement in standardized seizure frequency) as well as with respect to further efficacy parameters in paediatric patients with partial onset seizures.

The adverse event profile derived from part I and II of study 305 was generally consistent with previous data on ESL.

Rapporteur's overall conclusion and recommendation

Overall conclusion

The MAH did not propose any amendment of the product information.

Study 305 did not allow for conclusion of efficacy of ESL as adjunctive treatment in paediatric patients with refractory partial onset seizures and the current information given in the product information of Zebinix, that efficacy of eslicarbazepine acetate in children has not yet been established was considered by the CHMP further valid. However, the hitherto information that "no data are available" should be deleted with the next possible opportunity.

No new unique safety concerns occurred within this study. An update of the product information regarding safety was therefore not considered necessary at the time of this report.

Recommendation

It is recommended that the SmPC is amended as indicated below:

SmPC, section 4.2:

...

"Paediatric population

The safety and efficacy of eslicarbazepine acetate in children and adolescents below 18 years has not yet been established. ~~No data are available.~~

There is no need to amend the respective information of the PL, section 2 which reads:

...

"Children and adolescents

Zebinix is not to be given to children and adolescents."