SAFETY PROFILE OF ESLICARBAZEPINE ACETATE IN ELDERLY PATIENTS WITH FOCAL ONSET SEIZURES: FROM CLINICAL STUDIES TO 8 YEARS OF POST-MARKETING EXPERIENCE

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INTRODUCTION

Treatment of epilepsy in the elderly is challenging, due to high levels of comorbidity and polypharmacy, as well as age-associated physiological changes, which may affect the pharmacodynamics and pharmacokinetics of antiepileptic drugs (AEDs).[1,2] Moreover, information regarding the use of AEDs in the elderly is relatively scarce, because elderly individuals are routinely excluded from clinical trials.[3,4] Data from post-marketing surveillance therefore provide a valuable source of complementary evidence.

Eslicarbazepine acetate (ESL) is a once-daily (QD) AED that is approved in Europe as monotherapy in the treatment of partial-onset seizures, with or without secondary generalization, in adults with newly diagnosed epilepsy, and as adjunctive therapy in adults, adolescents and children aged >6 years with partial-onset seizures, with or without secondary generalization.[5] In the USA, ESL is approved for the treatment of partial-onset seizures in patients aged ≥4 years.[6]

We present the findings of a pooled analysis of ESL clinical studies that included elderly patients and an assessment of post-marketing safety data, in order to provide further evidence of the safety profile of ESL in elderly patients.

PURPOSE

To evaluate the safety of ESL in elderly patients with focal seizures, from clinical studies and during 8 years of post-marketing experience, and to compare the safety profile of ESL in elderly patients versus non-elderly patients.

MATERIAL AND METHODS

Study design

- Safety data were compared for elderly (≥65 years) versus non-elderly (<65 years) adult patients with focal seizures, obtained from two sources:
  - Double-blind and open-label Phase II/III clinical studies, comprising BIA-2093-201, -301(Part I–IV), -302(Part I-II), -303(Part I-II), -304(Part I), -311(Part I), and -401
    - Data were pooled and analyzed
  - Post-marketing safety data (from 01 October 2009 [first launch] to 21 October 2017)
    - Data were obtained from safety reports received spontaneously, from health authorities, literature, non-interventional studies, and other solicited sources as part of pharmacovigilance activities

Study assessments

- For clinical trial data, ESL safety was assessed by evaluating the rates and types of:
  - Treatment-emergent adverse events (TEAEs)
  - Treatment-related TEAEs (defined as at least possibly related)
  - Serious TEAEs
  - Treatment-related serious TEAEs
  - TEAEs leading to discontinuation
- For post-marketing data, ESL safety was assessed by evaluating the rates (% was calculated based on number of specific ADRs per total number of ADRs) and types of adverse drug reactions (ADRs) reported

Statistical analyses

- Data were compared for elderly (≥65 years) versus non-elderly (<65 years) adult patients
- Categorical and continuous variables were summarized using descriptive statistics
- Safety variables were compared for elderly versus non-elderly patients using the Chi-square test or Fisher's exact test, as appropriate

RESULTS

Study population

- Pooled analysis of ESL clinical studies included 120 elderly patients (≥65 years) and 1863 non-elderly patients (18–64 years)
  - 67 (55.8%) elderly patients and 934 (50.1%) non-elderly patients were male

ESL exposure

- In the pooled analysis of clinical studies, exposure to ESL was 81.1 person-years of treatment for elderly patients and 1916.2 person-years of treatment for non-elderly patients
- Estimated patient exposure from the time of ESL marketing authorization until 21 October 2017 was a total of 2,417,394 patient-months, corresponding to 201,450 patient-years*

Safety

Clinical study data

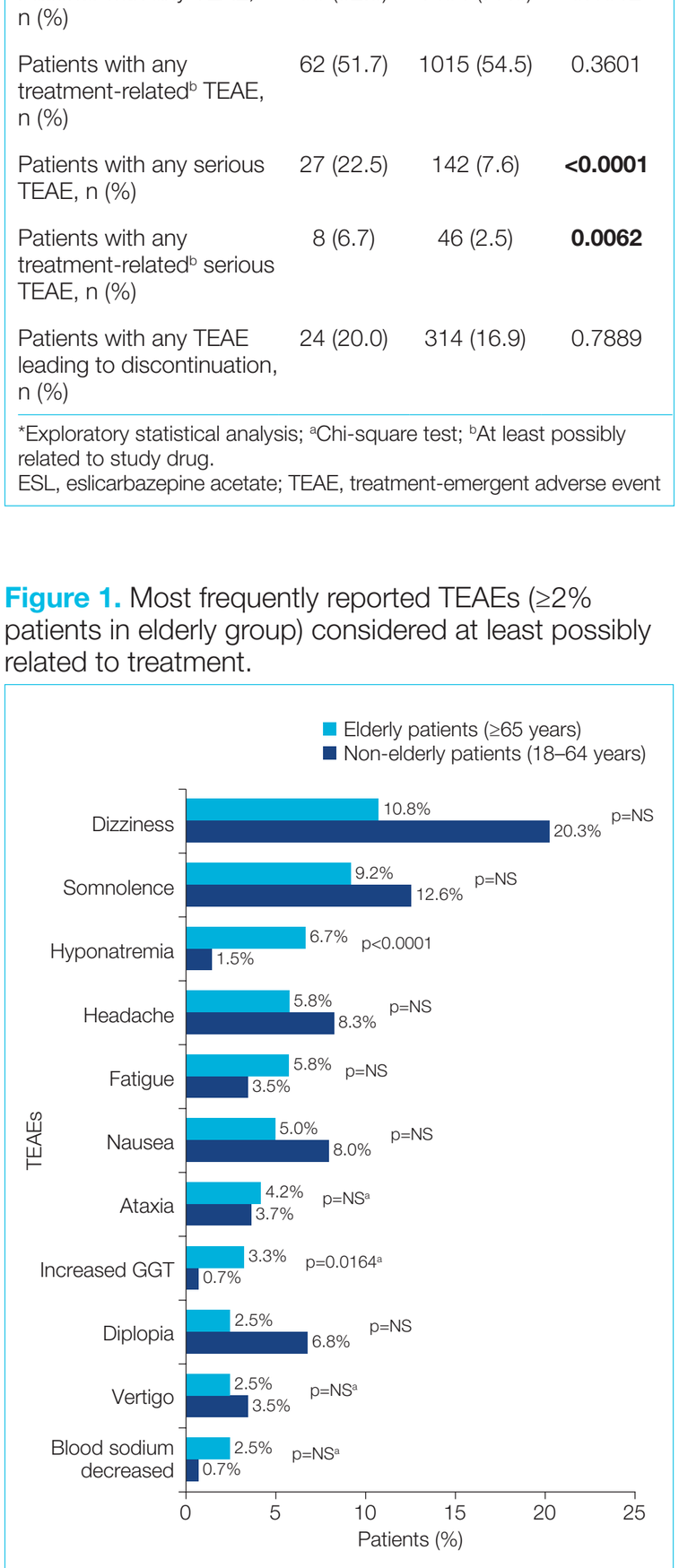
- Incidences of TEAEs, treatment-related TEAEs and TEAEs leading to discontinuation were similar for elderly and non-elderly patients (**Table 1**)
- Dizziness and somnolence were the most frequently reported treatment-related TEAEs in elderly and non-elderly patients (**Figure 1**)
  - Incidences of hyponatremia and increased gamma-glutamyltranserase were significantly higher in elderly than in non-elderly patients
- Incidences of serious TEAEs and treatment-related serious TEAEs were significantly higher in elderly patients than in non-elderly patients
  - The only treatment-related serious TEAE reported in ≥1% elderly patients was hyponatremia (n=2; 1.7%)
  - Hyponatremia was also reported as a treatment-related serious TEAE in two non-elderly patients (0.1%)

Table 1. Pooled analysis of ESL clinical studies: summary of TEAEs in elderly (≥65 years) and non-elderly (18–64 years) patients

	Elderly patients (N=120)	Non-elderly patients (N=1863)	p-value*[a]
Patients with any TEAE, n (%)	99 (82.5)	1434 (77.0)	0.1612
Patients with any treatment-related[b] TEAE, n (%)	62 (51.7)	1015 (54.5)	0.3601
Patients with any serious TEAE, n (%)	27 (22.5)	142 (7.6)	**<0.0001**
Patients with any treatment-related[b] serious TEAE, n (%)	8 (6.7)	46 (2.5)	**0.0062**
Patients with any TEAE leading to discontinuation, n (%)	24 (20.0)	314 (16.9)	0.7889

*Exploratory statistical analysis; [a]Chi-square test; [b]At least possibly related to study drug.
ESL, eslicarbazepine acetate; TEAE, treatment-emergent adverse event

Figure 1. Most frequently reported TEAEs (≥2% patients in elderly group) considered at least possibly related to treatment.



Statistical comparisons were conducted using the Chi-square test unless stated otherwise. [a]Fisher's exact test. GGT, gamma-glutamyltransferase; NS, not significant; TEAE, treatment-emergent adverse event

Post-marketing data

- After 8 years of post-marketing experience, 473 and 2406 ADRs/safety information were reported for elderly and non-elderly patients, respectively (**Table 2**)
- The most frequently reported ADRs (≥5% of total ADRs in either group) were hyponatremia (elderly 14.6% vs. non-elderly 6.8%) and seizure (2.1% vs. 5.8%)

Table 2. ESL post-marketing data: summary of ADRs/safety information reported in elderly (≥65 years) and non-elderly (18–64 years) patients

	Elderly patients	Non-elderly patients
Total number of ADRs, N	473	2406
Most frequently reported[a] ADRs, n (%)[b]		
Hyponatremia	69 (14.6)	163 (6.8)
Drug dose titration not performed[c]	33 (7.0)	129 (5.4)
Seizure	10 (2.1)	139 (5.8)
Dizziness	16 (3.4)	84 (3.5)
Off-label use[c]	16 (3.4)	53 (2.2)
Product use in unapproved indication[c]	23 (4.9)	45 (1.9)
Fatigue	6 (1.3)	46 (1.9)
Rash	6 (1.3)	45 (1.9)
Nausea	11 (2.3)	35 (1.5)
Somnolence	[<1.0%][d]	43 (1.8)
Blood sodium decreased	6 (1.3)	37 (1.5)
Inappropriate schedule of drug administration[c]	[<1.0%][d]	36 (1.5)
Headache	[<1.0%][d]	35 (1.5)
Drug ineffective[c]	[<1.0%][d]	31 (1.3)
Overdose[c]	[<1.0%][d]	29 (1.2)
Vomiting	5 (1.1)	23 (1.0)
Epilepsy	[<1.0%][d]	27 (1.1)
Fall	8 (1.7)	[<1.0%][e]
Confusional state	7 (1.5)	[<1.0%][e]
Cognitive disorder	6 (1.3)	[<1.0%][e]
Tremor	5 (1.1)	[<1.0%][e]
Malaise	5 (1.1)	[<1.0%][e]
Pruritus	5 (1.1)	[<1.0%][e]

[a]≥1% of total ADRs; [b]Percentage of total ADRs; [c]Safety information; [d]Frequency of ADR/safety information reported was <5, corresponding to percentage <1.0; [e]Frequency of ADR reported was <25, corresponding to percentage <1.0. ADR, Adverse drug reaction

- ADRs reported at a higher percentage of total ADRs for elderly versus non-elderly patients were hyponatremia, fall, confusional state, tremor, malaise and pruritus
- The percentage of reported ADRs that were serious was 42.3% and 31.9% for elderly and non-elderly patients, respectively

CONCLUSIONS

- Pooled analysis of data from clinical studies demonstrated that the safety of ESL in elderly patients (≥65 years) was generally similar to that observed in non-elderly patients (18–64 years).
  - Dizziness and somnolence were the most frequently reported treatment-related TEAEs in both elderly and non-elderly patients.
  - At least possibly related serious TEAEs were more common in the elderly population than in non-elderly patients.
  - Hyponatremia and increased gamma-glutamyltranserase were reported as treatment-related TEAEs by a significantly higher proportion of elderly versus non-elderly patients.
  - However, the exploratory statistical analysis and small number of elderly patients in clinical trials limit the comparative incidence data.
- With an estimated cumulative exposure of over 2 million patient-months worldwide, 232 ADRs related to hyponatremia have been reported.
- In patients with pre-existing renal disease leading to hyponatremia, or patients concomitantly treated with medicinal products that may lead to hyponatremia, sodium levels should be monitored during treatment with ESL.[5]
- The qualitative safety of ESL in elderly patients after 8 years of clinical experience was consistent with data obtained from clinical studies.

*For estimation of patient exposure, it was assumed that the ex-factory amounts delivered were entirely dispensed and actually all administered, and were used at the dosage regimen of 1 tablet per day, regardless of dose strength, as recommended in the ESL Summary of Product Characteristics.[5] Because ESL is intended for long-term therapy, exposure is calculated in patient-months (units divided by 30) and patient-years, rather than in number of treated patients.

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