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EXPERT REVIEW

A Review of Eslicarbazepine Acetate for the Adjunctive Treatment of Partial-Onset Epilepsy

Rajinder P. Singh and Jorge J. Asconapé

Department of Neurology, Stritch School of Medicine, Loyola University Medical Center, Maywood, Illinois 60153, USA.
Corresponding author email: jasconape@lumc.edu

Abstract: Eslicarbazepine acetate (ESL) is a novel antiepileptic drug indicated for the treatment of partial-onset seizures. Structurally, it belongs to the dibenzazepine family and is closely related to carbamazepine and oxcarbazepine. Its main mechanism of action is by blocking the voltage-gated sodium channel. ESL is a pro-drug that is rapidly metabolized almost exclusively into S-licarbazepine, the biologically active drug. It has a favorable pharmacokinetic and drug-drug interaction profile. However, it may induce the metabolism of oral contraceptives and should be used with caution in females of child-bearing age. In the pre-marketing placebo-controlled clinical trials ESL has proven effective as adjunctive therapy in adult patients with refractory of partial-onset seizures. Best results were observed on a single daily dose between 800 and 1200 mg. In general, ESL was well tolerated, with most common dose-related side effects including dizziness, somnolence, headache, nausea and vomiting. Hyponatremia has been observed (0.6%–1.3%), but the incidence appears to be lower than with the use of oxcarbazepine. There is very limited information on the use of ESL in children or as monotherapy.

Keywords: eslicarbazepine, licarbazepine, dibenzazepine, voltage-gated sodium channel, partial-onset seizures, epilepsy

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Introduction

Even though antiepileptic drugs have made a significant impact in the treatment epilepsy over the last three decades, about 30% of adults and 25% of children with epilepsy still have inadequate seizure control.[1,2] Among those patients with intractable epilepsy a very high proportion suffer from partial seizures. The second generation of antiepileptic drugs, first introduced in the early 1990s, has been a welcome addition to the therapeutic armamentarium for the treatment epilepsy. For the most part, these drugs have demonstrated better tolerability and a more favorable pharmacokinetic profile than the "classic" ones, making their use much simpler for the practicing physician. Unfortunately, as far comparative efficacy is concerned, these drugs have been rather disappointing, with an overall efficacy very similar to that of the older agents. Therefore, there is still a great need for better, more effective antiepileptic drugs for the treatment of epilepsy.

Eslicarbazepine acetate (ESL) is a novel antiepileptic drug with a spectrum of action essentially limited to partial-onset and generalized tonic-clonic seizures. This paper will review in some detail the pivotal clinical trials that have established the efficacy and tolerability of ESL as adjunctive therapy in patients with partial-onset epilepsy, while providing a more succinct summary of its chemistry, mechanism of action and clinical pharmacokinetics.

Structure and Chemistry

Eslicarbazepine acetate, (S)-(-)-10-acetoxy-10, 11-dihydro-5H-dibenzazepine-5-carboxamide (S-licarbazepine; BIA 2-093; Stedesa® in the United States; Zebinix®, Exalief® in Europe), is a third generation antiepileptic drug that belongs to the dibenzazepine family (Fig. 1), which also includes carbamazepine (CBZ) and oxcarbazepine (OXC).[3] Structurally, ESL shares the dibenzazepine nucleus with CBZ and OXC, differing from these drugs by a 5-carboxamide substitute at the 10,11 position.[4] This configuration conveys ESL some special characteristics. Unlike CBZ, ESL is not metabolized into the CBZ 10,11-epoxide, an active and potentially toxic compound. As a result, ESL has very low enzyme-inducing activity of the cytochrome P450 enzymatic system and does not induce its own metabolism. ESL differs from OXC in that it is metabolized almost exclusively to the (S)-enantiomer (designated as S-licarbazepine) with less than a 5% chiral conversion to the (R)-enantiomer, whereas OXC is converted to both (S)- and (R)- enantiomers in about a 4–5:1 proportion (Fig. 2).[4–6] ESL was developed with the expectation that S-licarbazepine would be more effective, better tolerated, and able to cross the blood brain barrier more efficiently than R-licarbazepine.[7]

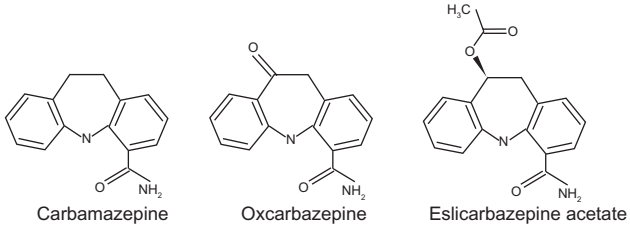

Figure 1. Chemical structure of the dibenzazepine family.

Mechanism of Action

ESL works by blocking the voltage-gated sodium channel, which play an essential role in the generation and propagation of the epileptic discharge. The voltage-gated sodium channel has three functional states: 1) deactivated or resting state where the channel is closed but responsive to a depolarizing stimulus, 2) state of depolarization, 3) inactivated state, a brief period following a depolarization during which the channel is closed and unresponsive. In vitro studies demonstrate that ESL, like CBZ, competitively interacts with the neurotoxin site 2 of the voltage-gated sodium channel, with a higher affinity for the inactivated state than the resting state.[8,9] This results in a more selective blocking of the rapid repetitive firing of neurons as seen in the epileptic process compared to more physiologic neuronal firing rates.[8,9]

In animal models, ESL has a very similar profile to CBZ and OXC. It showed efficacy in seizures induced by proconvulsant agents such as metrazole, bicuculline, 4-amino-pyridine, latruncullin, and picrotoxin.[10–12] ESL has also shown to be as effective as CBZ in the amygdala-kindled rat model.[10] This activity profile predicts efficacy in partial and generalized tonic-clonic seizures in humans. In these models, ESL was equipotential to CBZ and more potent than OXC. When ESL was compared with either CBZ or OXC, it showed less neurological impairment in rats and was less toxic to cultured hippocampal neurons.[4,13]

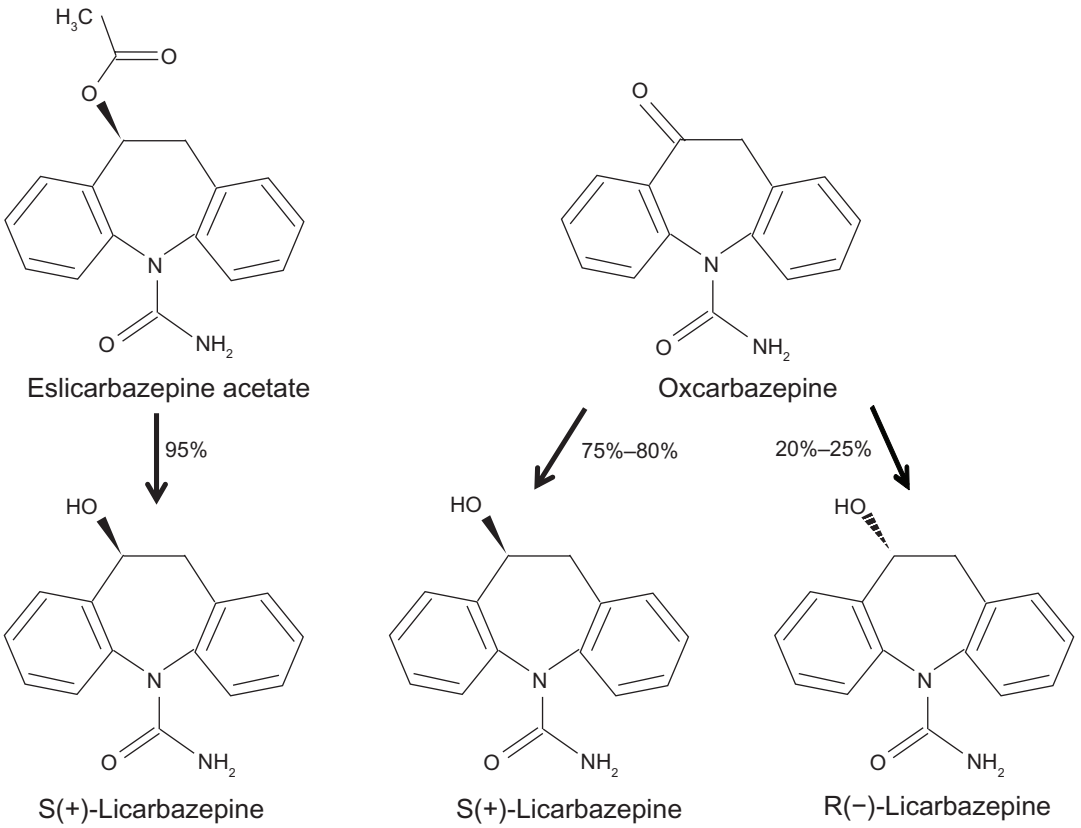

Figure 2. Metabolism of eslicarbazepine acetate and oxcarbazepine.

Pharmacokinetics

ESL acetate is an oral prodrug that is rapidly and extensively metabolized by the liver via a hydrolytic first-pass metabolism into S-licarbazepine, the biologically active drug. The plasma level of the prodrug remains below quantification.[14] ESL is well absorbed after oral administration with a bioavailability about 16% higher than that observed after an equivalent dose of OXC.[15] The absorption of ESL was not affected by a high fat content meal or 10 hours of fasting,[16] nor by gender[17] or age.[14] The peak plasma concentration (t_{max}) is achieved in 1–4 h. Plasma protein binding is low (<40%) and independent of concentration. The half-life is 13–20 hours and steady-state plasma levels are attained after 4–5 days.[18] ESL displays linear kinetics at doses of 400 mg to 1200 mg/day.[10] ESL is eliminated predominantly by renal excretion, with 91% of the drug recovered in urine following an oral dose.[10] ESL acetate is rapidly converted by hydrolysis to ESL. In healthy volunteers, of the dose recovered in the urine 52% corresponded to ESL and 41% to ESL-glucuronide.[20] ESL has a clearance rate of 20 to 30 ml/min, with 20% of the dose recovered in the urine after 12 hours and 40% within 24 hours.[10,18] Pharmacokinetic parameters of ESL are summarized in Table 1.

Hepatic impairment

The clearance of ESL was not significantly affected in the presence of mild or moderate hepatic failure, and dose adjustments are usually not necessary in this setting.[19] The pharmacokinetics of ESL, however, has not been studied in patients with severe hepatic impairment.

Table 1. Pharmacokinetics of eslicarbazepine acetate.

Bioavailability	Complete
Peak plasma concentration	1–4 h
Plasma protein binding	<40%
Half-life	13–20 h
Serum concentrations	5–9 mcg/ml
“Therapeutic range”	Not established
Plasma clearance	20–30 ml/min
Elimination	Hydroxylation, conjugation –> renal excretion

Renal impairment

Patients with mild renal impairment demonstrated slightly slower elimination rates compared to normal volunteers (10.2 ml/min vs. 17. 3 ml/min respectively). As expected, patients with moderate or severe renal impairment showed much lower clearance rates (3.7 ml/min and 1.5 ml/min respectively).[20] Dose adjustments are generally required in the presence of moderate or severe renal impairment (creatinine clearance <50 ml/min).

Drug-Drug Interactions

ESL has a favorable drug-drug interaction profile due to its low protein binding and minimal effect on the hepatic cytochrome P450 enzymatic system (CYP). In vitro studies have shown that ESL has a moderate inhibitory effect on the CYP 2C19, and no relevant inhibitory effect on the CYP 1A2, CYP 2A6, CYP 2B6, CYP 2D6, CYP 2E1, CYP 3A4, CYP 2C9.

Concomitant use with phenytoin resulted in a 33% decrease of the ESL exposure. The underlying mechanism is probably enzymatic induction of glucuronidation, and other inducers such as phenobarbital or CBZ have a similar effect. Steady dosage of ESL increased the levels of phenytoin and phenobarbital, possibly due to inhibition of the CYP 2C19. No significant pharmacokinetic interactions were found in an open-label study of 16 healthy volunteers receiving ESL (1200 mg once daily) and lamotrigine (150 mg once daily) for 19 days.[21] Concomitant use of ESL 1200 mg once daily and topiramate 200 mg once daily showed 18% decreased in topiramate bioavailability but no alteration in the ESL exposure. This effect, however, was not clinically significant and dose adjustments are probably not necessary.[22] No significant drug-drug interactions were found between ESL and levetiracetam or valproate.

Oral contraceptives

Patients who are taking ESL and hormonal contraceptives need to be vigilant as ESL interact with these agents.[10] Female patients taking ESL at a dose of 1200 mg once daily were found to have a 37% and 42% decrease in the systemic exposure to levonorgestrel and ethinyloestradiol respectively.[23]

Other meds

ESL had no significant effects on the pharmacokinetics of metformin,[24] digoxin[25] or warfarin.[26]

Efficacy

The efficacy of ESL as adjunctive therapy in patients with refractory partial-onset epilepsy has been adequately studied in three randomized, double-blind, placebo-controlled, add-on pivotal clinical trials.

In an initial exploratory study by Elger et al (2007), 143 patients, aged between 18–65 years, with ≥4 partial-onset seizures/month, were randomly assigned to three treatment groups: ESL once daily (n = 50), ESL twice daily (n = 46), and placebo (n = 47).[5] Patients in the active arms were started on 400 mg/d (on one or two divided doses) and the doses increased to 800 mg/d and 1200 mg/d at 4-week intervals. The maximum total daily dose achieved was 1200 mg. The duration of the active phase was 12 weeks, followed by a 1-week tapering-off phase. Concomitant antiepileptic drugs were continued unchanged during the study. The proportion of patients with a ≥50% reduction in the frequency of seizures ("responder" rate) was the primary end point.[5] Of 144 patients enrolled in the study, 143 were included in the intent to treat (ITT) population, 113 completed the 12-week treatment phase, and 110 completed the entire study.[5] The responder rate of the 12-week treatment period vs. baseline in the ITT population showed a statistically significant difference in favor of the once-daily group compared to the placebo group (54% vs. 28% respectively; $P = 0.008$). The difference between the twice-daily and the placebo group, however, was not statistically significant (41% vs. 28% respectively, $P = 0.12$). Analysis of the primary variable of the per protocol (PP) population (n = 109) showed similar results: a statistically significant difference between the once-daily population vs. placebo (61% vs. 38% respectively; $P = 0.04$), but not between the twice-daily and the placebo groups (53% vs. 38% respectively; $P = 0.17$). The percentage of seizure-free patients on the last 4 weeks of the treatment period was 24% in both the once-daily and twice-daily groups vs. 9% in the placebo group, a statistically significant difference.[5] The most common side effects reported were headache, dizziness, nausea, somnolence and vomiting. There were no serious

adverse effects reported. The reason for the difference in efficacy between the once-daily and twice-daily groups remains unclear. The authors speculate that the higher C_{max} reached in the once-daily group could account for the difference.

In a follow-up, larger, multicenter, parallel-group clinical trial, Elger et al (2009) assessed the efficacy and safety of ESL as adjunctive therapy in adult patients with refractory partial seizures with ≥4 seizures per month despite therapy with 1–2 antiepileptic drugs.[27] In this study, following a single-blind, 8-week baseline phase, patients were randomized to placebo (n = 102) or once-daily ESL 400 mg (n = 100), 800 mg (n = 98), 1200 mg (n = 102) in a double-blind treatment phase. ESL was started at a 400 mg/d dose and titrated by 400-mg weekly increases. Then, patients were kept on QD 400 mg, 800 mg, or 1200 mg for 12 weeks. The primary analysis of efficacy was based on the intent-to-treat population. The primary efficacy variable was seizure frequency, standardized to a frequency per 4 weeks over the maintenance period. Secondary efficacy variables included proportion of responders (patients with ≥50% reduction in standardized seizure frequency); relative reduction in standardized seizure frequency; number of days with seizures; proportion of seizure-free patients; and proportion of patients with ≥25% exacerbation in standardized seizure frequency compared to baseline. Standardized seizure frequency per 4 weeks in the ITT population was significantly lower than placebo in the 800-mg ($P = 0.0028$) and 1200-mg ($P = 0.0003$) groups, but not in the 400-mg group. The responder rate was also significantly higher in the 1200-mg (43%; $P = 0.0009$), and 800-mg (34%; $P = 0.0359$) groups compared to placebo (20%). The responder rate difference in the 400-mg group (23%) was not significant. The median relative reduction in seizure frequency was 16% (placebo), 26% (400 mg), 36% (800 mg), and 45% (1200 mg). Seizure freedom rates were as follows: placebo (2%), 400-mg (2%; n.s.), 800-mg (4%; n.s.); 1200-mg (8%; $P < 0.05$). Similar efficacy results were observed in patients receiving CBZ as a concomitant antiepileptic drug. Most common adverse events (occurring in >10% of patients) were headaches, dizziness and diplopia. Discontinuation rates due to adverse events were: 3.9% in the placebo group, and 4%, 8.2% and 19.6% in the 400-, 800-, and 1200-mg groups respectively.

The study by Gil Nagel et al used a very similar design: a multicenter, randomized, add-on, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of once-daily ESL as adjunctive therapy in patients with refractory partial-onset seizures while on 1–3 other concomitant antiepileptic drugs.[28] Patients were required to have ≥4 seizures over an 8-week period prior to entry in the study as well as ≥4 seizures during the 8-week observation phase of the study. Patients were randomized to placebo (n = 87), ESL 800 mg (n = 85) and 1200 mg (n = 80), with a 2-week titration phase and a 12-week maintenance period. Efficacy assessments were based on an intent-to-treat population. The primary efficacy variable was the standardized seizure frequency per 4-week periods, comparing the change over the 12-week maintenance period to baseline. Secondary end points included responder rate, relative reduction in seizure frequency, number of days with seizures, distribution of seizure reduction, proportion of seizure free patients, and proportion of patients with an exacerbation in seizure frequency ≥25% compared to baseline. There was significant decrease in seizure frequency in both ESL treatment groups when compared to placebo ($P < 0.005$). The responder rate was 34.5% in the 800-mg group ($P = 0.106$), 38% in the 1200-mg group ($P = 0.020$), and 22.6% in the placebo group.[27] The median relative reduction in standardized seizure frequency was higher in the 800-mg (37.9%) and 1200-mg (41.9%) groups than in the placebo (17.0%) group. The proportion of seizure-free subjects was higher in the 800-mg (4.8%) and 1200-mg (3.9%) groups compared to the placebo (1.2%) group, but these differences did not reach statistical significance. Most common adverse events (reported in >10% of subjects) included dizziness, somnolence, headache and nausea.

The study by Ben-Menachem et al, again, investigated the efficacy and safety of once-daily ESL as add-on treatment for adult patients with ≥4 partial per 4-week despite treatment with 1–3 antiepileptic drugs.[7] It used a double-blind, parallel-group, multicenter design, with an 8-week observational baseline followed by a 14-week treatment phase.

Patients were randomized to placebo (n = 100) or once-daily ESL 400 mg (n = 96), 800 mg (n = 101) or 1200 mg (n = 98). Primary efficacy variable was standardized seizure frequency per 4-week periods. Secondary efficacy variables included proportion of responders, relative reduction from baseline in seizure frequency, number of days with seizures, proportion of seizure-free patients, and proportion of patients with an exacerbation in seizure frequency ≥25% compared to baseline. An intent-to-treat analysis was utilized. Seizure frequency per 4-week period was significantly lower in the ESL 800 mg and ESL 1200 mg ($P \leq 0.001$) groups. Responder rate was 13.0% in the placebo group, 16.7% in the ESL 400 mg, 40.0% in the ESL 800 mg ($P < 0.001$), and 37.1% in the ESL 1200 mg ($P < 0.001$). The median relative reduction in seizure frequency rates were significantly higher in the 800 mg (32.6%; $P < 0.001$) and 1200 mg (32.8%; $P < 0.001$) groups compared to placebo (0.8%). Proportion of seizure-free subjects was 1% (placebo), 1% (400 mg; n.s.), 8% (800 mg; $P < 0.05$), and 4% (1200 mg; n.s.). Discontinuation rates due to adverse events were 3.0% (placebo), 12.5% (400 mg), 18.8% (800 mg) and 26.5% (1200 mg). Side effects reported in >5% of subjects included dizziness, somnolence, headache, nausea, diplopia, abnormal coordination, vomiting, blurred vision and fatigue. Incidence of adverse events in the study was considerably higher than in the other two pivotal clinical trials.

In summary, these studies have shown that ESL is effective and well tolerated as adjunctive therapy in patients with partial-onset seizures.[7,27,28] Single dosing is as effective, if not more effective, than BID use, with the optimal dose ranging from 800 mg to 1200 mg once daily. At these doses the responder rates ranged from 34% to 43% (Fig. 3), suggesting that the efficacy of ESL in patient with refractory partial seizures is similar to that of most of the second generation antiepileptic drugs.

Efficacy and safety in pediatric patients

There is very limited information on the efficacy of ESL in the pediatric age group. Almeida et al explored the pharmacokinetics, efficacy and tolerability of ESL in children aged 2–6 years (group 1, n = 12), 7–11 years (group 2, n = 8), and 12–17 years (group 3, n = 11), in an open-label, add-on, single center design.[29] Subjects were taking 2–3 antiepileptic drugs. A 4-week observational period was followed by 3 consecutive 4-week periods at doses of 5 ml/kg/day, 15 ml/kg/day, 30 mg/kg/day (not to exceed 1800 mg/d). This was followed by a 4-week tapering down. The number of seizures during the baseline period was highly variable with

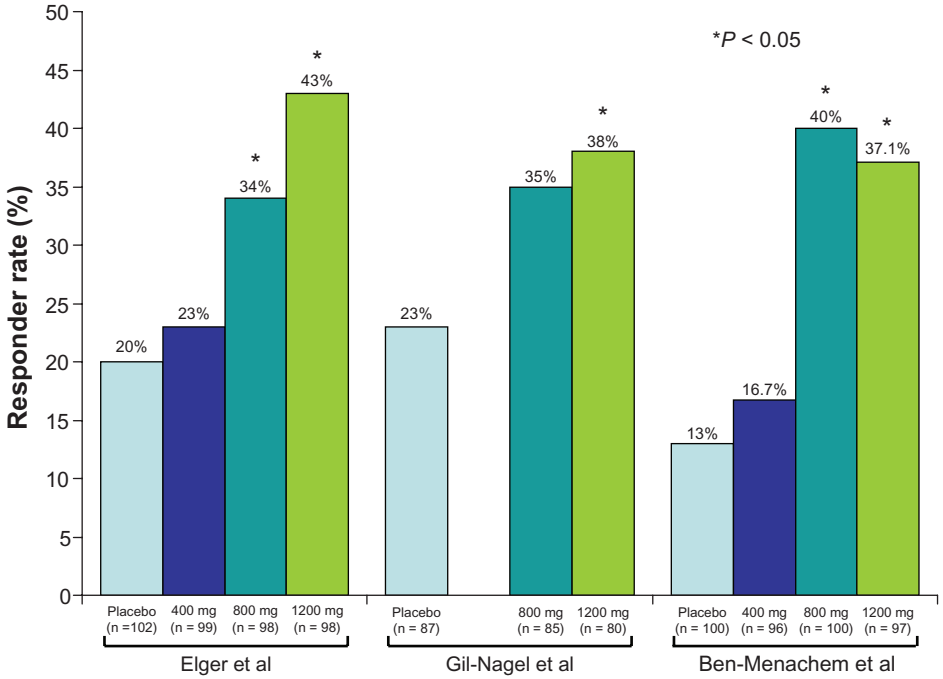

Figure 3. Eslicarbazepine acetate: responder rates (proportion of subjects with a ≥50% reduction in seizure frequency) in the pivotal clinical trials.[7,27,28]

1077 seizures in group 1, 267 seizures in group 2, and 49 seizures in group 3.

ESL acetate was rapidly hydrolyzed to ESL and maximum plasma concentration was reached by 0.5–3 hours of the dosage in all age groups. The extent of systemic exposure (AUC) was age-dependent, with higher plasma clearance rates in younger children when compared to adolescents.

A relative dose-dependent decrease in seizure frequency was seen in group 1 (–28% with 5 m/kg/d, –24% with 15 ml/kg/d, and –40% with 30 ml/kg/d) and group 3 (–17% with 5 m/kg/d, –31% with 15 ml/kg/d, and –43% with 30 ml/kg/d). One patient in each of these two groups became seizure free. There was no clear dose-dependent decrease in seizure frequency seen in group 2 (–11% with 5 ml/kg/day, –5% with 15 ml/kg/day, and –12% with 30 mg/kg/d). Overall, ESL at doses of 5 ml/kg/d and 15 ml/kg/d was well tolerated, but a higher incidence of adverse effects was seen at 30 ml/kg/d.[29]

Safety and Toxicity Profile

The most common side effects observed regardless of amount or frequency of dosage were dizziness, somnolence, headache, nausea, diplopia and vertigo.[5,7,27,28] The main adverse events leading to discontinuation of the medication in clinical trials included dizziness, abnormal coordination, and nausea.[7,27,28] These side effects appear to be dose-dependent (Table 2).

The above dose-dependent side-effect profile is very similar to that of other sodium channel blockers such as CBZ, OXC or lamotrigine. A pharmacodynamic interaction leading to increased clinical toxicity has been well documented in clinical practice when two or more of these drugs are used concomitantly. It should be noted that a significant proportion of patients in the clinical trials were taking other sodium channel blockers, most commonly CBZ. Therefore, it is likely that the incidence of dose-dependent side-effects in the pivotal clinical trials may have been overestimated. It is likely that ESL will be better tolerated when associated with antiepileptic drugs with a different mechanism of action such as levetiracetam, topiramate, valproate or pregabablin.

Hyponatremia remains one of the most common reasons leading to the discontinuation of therapy in patients treated with OXC. Therefore, there is hope that ESL may be associated with a lower risk for hyponatremia. Hyponatremia has been observed in 0.6%–1.3% of patients treated with ESL during the pre-marketing clinical trials.[5,7,27,28] In the study by Ben-Menachem et al, of 295 patients given ESL only 4 (1.3%) developed hyponatremia versus none in placebo group.[7] However, three of the four patients with hyponatremia were also taking CBZ.[7] In the study by Elger et al (2009), the sodium levels seemed to have an inverse correlation with ESL dosage. By the end of the 12-week maintenance phase the median (range) sodium concentrations were: placebo group 141.0 (131–149) mmol/L, 400-mg 141.0 (130–146) mmol/L, 800-mg 140.0 (123–148) mmol/L, and 1200-mg 140.5 (127–145) mmol/L.[27] In this study, only one patient was found to have a sodium level <125 mmol/L. This was a 31-year-old male on CBZ therapy who presented with a sodium level of 133 mmol/L at randomization. By the end of the maintenance phase of the study (while on ESL 800 mg/d and CBZ 1000 mg/d) the sodium level was 123 mmol/L. His sodium level returned to normal (136 mmol/L) after ESL was tapered-off.[27]

Table 2. Summary of the most common adverse events reported in the three pivotal clinical trials.[7,27,28]

Adverse event (AE)	Number (%) of patients			
	Placebo (n = 289)	ESL 400 mg/d (n = 196)*	ESL 800 mg/d (n = 284)	ESL 1200 mg/d (n = 280)
Any AE	134 (46.4)	119 (60.7)	178 (62.7)	189 (67.5)
Dizziness	21 (7.3)	26 (13.2)	60 (21.2)	81 (28.9)
Headache	25 (8.7)	17 (8.7)	29 (10.2)	38 (13.6)
Diplopia	5 (1.7)	10 (5.1)	23 (8.1)	24 (8.6)
Nausea	5 (1.7)	8 (4.1)	18 (6.3)	27 (9.6)
Somnolence	27 (9.3)	21 (10.7)	37 (13)	42 (15)
AEs leading to discontinuation	13 (4.5)	16 (8.2)	34 (12)	55 (19.6)

Note: *Study from Gil-Nagel et al[27] did not include a ESL 400 mg/d arm.

More studies are needed to dilucidate if ESL has a lower incidence of hyponatremia than OXC.

Skin rash has been reported in approximately 3% patients treated with ESL in the preclinical trials.[7,27,28] In the SANAD study, a large efficacy and safety monotherapy trial in patients with new-onset epilepsy, the incidence of rash was 7% for CBZ and 6% for OXC.[30] This data suggests that the incidence of rash may be lower with ESL than with CBZ or OXC, which would constitute a significant advantage for this drug in clinical practice. More data, however, is necessary before any conclusions can be drawn.

Electrocardiographic changes consisting of a mild prolongation of the PR interval has been observed in patient receiving ESL.[23] ESL should not be used in patients with 2nd and 3rd degree heart block, and used with caution when co-administered with other drugs that can prolong the PR interval.[23]

Clinical Use

ESL has been approved for use in the European Union by the European Medicines Agency (EMEA) and is currently under review by the Food and Drug Administration (FDA) in the United States. It is indicated as adjunctive therapy for the treatment of partial seizures in adults. Monotherapy trials are currently being performed. The spectrum of action of ESL is similar to that of CBZ and OXC and limited to partial and generalized tonic-clonic seizures. It is not expected to be effective against absence or myoclonic seizures.

The drug is available as liquid suspension or tablet form in strengths of 400 mg, 600 mg, and 800 mg. Both formulations have the same bioequivalence.[15] The recommended dose in adults is 800 mg/d. The drugs should be started at a dose of 400 mg/d for 1–2 weeks before reaching the maintenance dose. Based on the individual clinical response, the dose can be increased to 1200 mg/d. Plasma levels have a linear correlation with the dose, but a "therapeutic range" has not been established. In the clinical trials mean ESL plasma levels were approximately 5 mcg/ml at 800 mg/d and 9 mcg/ml at 1200 mg/d.[27] ESL is eliminated mostly by renal excretion and dose adjustments are needed for patients with Clcr between 30–60 ml/min. It should be used with great caution in patients with Clcr $<$ 30 ml/min.[23] No dose adjustment is generally needed in mild or moderate hepatic impairment; however, there are no studies on the disposition of ESL in severe hepatic impairment.[19] The most common side effects include dizziness, somnolence, headache, nausea and vomiting.[28] Rash was observed in about 1% of patients treated with ESL. Overall, the risk for hyponatremia appears to be low (about 1%) and most cases are asymptomatic. The risk of hyponatremia is increased with a higher dose of ESL, pre-existing renal disease or concomitant use of other medications that can lower the sodium.

Summary

ESL acetate is a novel voltage-gated sodium channel blocker structurally related to CBZ and OXC. It has proven efficacious as adjunctive therapy in adult patients with partial-onset epilepsy. ESL has a favorable tolerability profile and is preferably used in a once-daily dosing. It has a better pharmacokinetic profile than CBZ with low potential for drug-drug interactions and no autoinduction of metabolism. It may be associated with lower rates of hyponatremia than CBZ or OXC, and may have a lower incidence of allergic rash as well. Comparative efficacy trials against other antiepileptic drugs are lacking, but the efficacy, based on the preclinical trials of the other antiepileptic drugs, appears to be similar. The most commonly reported adverse effects include dizziness, somnolence, headache nausea and vomiting. There is limited data available in children, and monotherapy use.[29]

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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