



## Eslicarbazepine acetate: a new promising antiepileptic agent

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### ABSTRACT

Eslicarbazepine acetate is a third generation, single enantiomer [(S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide] member of the commonly prescribed first-line antiepileptic drugs (AEDs), formerly known as BIA 2-093, is a novel central nervous system (CNS)-active compound with anticonvulsant activity. It is a prodrug which is activated to eslicarbazepine (S-licarbazepine), an active metabolite of oxcarbazepine. Eslicarbazepine acetate is used as an adjunctive therapy in adult patients with partial onset seizures. It behaves as a voltage-gated sodium channel (VGSC) blocker and is currently marketed for the treatment of epilepsy. Eslicarbazepine acetate shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11-position. This molecular variation results in differences in metabolism, preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide. This drug is considered as an adjunct to carbamazepine and oxcarbazepine.

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### Introduction

Epilepsy is one of the most common neurological diseases, affecting approximately 1 in 100 people<sup>[1]</sup>. Treatment of partial-onset seizures, the most common type of epilepsy, presents a constant challenge - up to 58% of patients with partial-onset seizures do not achieve seizure control with current antiepileptic drugs. Patient compliance with antiepileptic agents represents a significant area of unmet need, with poorly compliant patients more likely to have breakthrough seizures and have higher mortality risk. Additionally, patients with epilepsy often suffer from other concomitant diseases, further complicating the management of these patients. Finally, adverse events, such as dizziness and somnolence, are highly prevalent with existing antiepileptic agents and may affect as many as 97% of patients. Epilepsy is characterized by abnormal firing of impulses from nerve cells in the brain. In partial-onset epilepsy, these bursts of electrical activity are initially focused in specific areas of the brain, but may become more generalized, with symptoms varying according to the affected areas. Nerve impulses are triggered via voltage-gated sodium channels in the nerve cell membrane.

Epilepsy is a chronic disease that requires long-term treatment. The World Health Organisation (WHO) estimates that around 50 million people in the world have epilepsy at any one time, which is roughly 1% of the world population. Recent studies have shown that up to 70% of newly diagnosed children and adults with epilepsy in both developed and developing countries can be successfully treated (i.e. their seizures can be completely controlled for several years) with AEDs. However, despite a broad range of AEDs available on the market, roughly 30-40% of patients with epilepsy are uncontrolled with available treatment and a further 25% suffer from significant adverse effects. This is due to poor response and to the associated toxicities of available antiepileptic drugs<sup>[2]</sup>.

#### Role of new antiepileptic drugs:

The major factors that influence the selection of antiepileptic drugs are data on efficacy, tolerability, safety, and

pharmacokinetics as they emerge from clinical trials and experience. In addition, one cannot disregard differences in costs, in particular between drugs with similar efficacy. These differences are highly significant for AEDs, although they may vary somewhat between countries<sup>[3]</sup>. Adverse events, such as light-headedness (dizziness), somnolence (sleepiness), and cognitive slowing, are highly prevalent with existing antiepileptic agents and may affect as many as 97% of patients. The development of eslicarbazepine acetate was based on the view that S-licarbazepine would be a more effective component, have fewer adverse effects, and cross the blood brain barrier more efficiently than R-licarbazepine. Similar to oxcarbazepine, a main distinction between eslicarbazepine acetate and carbamazepine is that eslicarbazepine lacks a toxic epoxide.

Hence, there is a need for new anti-epileptic agents that offer effective reduction in seizure frequency combined with a favourable safety profile<sup>[4]</sup>.

#### Eslicarbazepine acetate

The active substance is chemically designated as (S)-10-Acetoxy-10, 11-dihydro-5Hdibenz [b,f]azepine-5-carboxamide. Eslicarbazepine acetate has one chiral centre, so it is optically active. It is synthesized as the S-enantiomer with the (S)-configuration at C<sub>10</sub>. It is white to off-white, non-hygroscopic, odourless crystalline solid. Under physiological conditions eslicarbazepine acetate is a non ionisable compound. Hydrolysis of the ester group occurs at low and high pH (1.2 and 10, respectively). It melts at 184 – 187 °C, with decomposition. No polymorphs is present which is confirmed by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot stage microscopy, spectroscopy (FT-Raman and FTIR), and moisture sorption/desorption analysis<sup>[5]</sup>.

#### Pharmacodynamics of eslicarbazepine

##### Mechanism of action:

The precise mechanism by which eslicarbazepine acetate exerts its antiepileptic effects remains to be fully elucidated. Electrophysiological studies indicate that both eslicarbazepine

acetate and its active metabolites (S-licarbazepine, R-licarbazepine and oxcarbazepine) competitively interact with site 2 of the inactivated state of a voltage-gated sodium channel (VGSC), preventing its return to the active state and repetitive neuronal firing. Therefore, eslicarbazepine acetate is supposed to act as a voltage-gated sodium channel blocker. Eslicarbazepine acetate has a much higher affinity for the inactivated state of the channel compared with the resting state which means it is less likely to interfere with normal neuronal function [6].

Preclinical experiments suggest that both Eslicarbazepine acetate and eslicarbazepine was tested in several animal seizure models predictive of anticonvulsant efficacy, such as the maximal electroshock seizure test in rats and mice and the corneal kindling in mice. Eslicarbazepine acetate also showed protective effects against seizures induced by several chemoconvulsants in rats or mice, namely metrazole, bicuculline, picrotoxin, and 4-aminopyridine (4-AP) [5].

#### Pharmacokinetics of eslicarbazepine acetate

##### Absorption:

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Following oral administration, plasma levels of eslicarbazepine acetate usually remain below the limit of quantification. Eslicarbazepine  $t_{max}$  is attained at 2-3 hours (h) post-dose. Bioavailability is considered high since the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose and the main metabolite eslicarbazepine was responsible for more than 95% of systemic exposure after administration of eslicarbazepine acetate [5, 6].

##### Distribution:

The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent from concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin and tolbutamide. The binding of warfarin, diazepam, digoxin, phenytoin and tolbutamide was not significantly affected by the presence of eslicarbazepine [6].

##### Metabolism:

Eslicarbazepine acetate is rapidly and extensively biotransformed to eslicarbazepine (S-licarbazepine) by hydrolytic first-pass metabolism. The apparent half-life of eslicarbazepine in healthy subjects and epileptic adults is 10-20 h and 13-20 h, respectively. Peak plasma concentrations ( $C_{max}$ ) of eslicarbazepine are attained at 2-3 h post-dose and steady state of plasma concentrations is attained after 4-5 days of QD dosing, consistent with an effective half-life in the order of 20-24 h. Minor metabolites in plasma are R-licarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

In total, eslicarbazepine acetate and its glucuronide conjugates correspond to 92% of the total drug material excreted in urine. Eslicarbazepine acetate has minimal interaction with the cytochrome P450 liver enzymes, thereby decreasing the risk for drug-drug interactions compared to carbamazepine and oxcarbazepine. In *in vitro* studies of human liver microsomes, eslicarbazepine acetate appeared to have no relevant inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4, or CYP2C9 and only a moderate inhibitory effect on CYP2C19 [6]. Furthermore, no differences in the pharmacokinetics of eslicarbazepine or its metabolites observed in case of hepatic impairment. Therefore, patients with mild to

moderate liver impairment treated with eslicarbazepine acetate do not require dosage adjustment [7].

In studies with eslicarbazepine in fresh human hepatocytes a mild activation of UGT1A1 mediated glucuronidation has been observed [8].

##### Excretion:

Eslicarbazepine acetate metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide correspond to more than 90% of total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate [6].

##### Therapeutic indications:

Eslicarbazepine acetate is used as an adjunctive therapy in adult patients with partial onset seizures.

##### Dose:

Eslicarbazepine acetate reduced epileptic seizure frequency significantly on a sustained basis. Eslicarbazepine acetate (Zebinix) can be given as a true one tablet once a day regimen. The median daily dose of eslicarbazepine acetate throughout this one year treatment is 800mg [1].

##### Adverse effects

Adverse drug reactions of eslicarbazepine are limited and mild to moderate in nature. These include dizziness, somnolence, nausea and headache [8].

##### Drug interactions

Pharmacokinetic interactions between eslicarbazepine acetate and phenytoin, digoxin, warfarin, lamotrigine, topiramate, oral contraceptives, carbamazepine, valproate, levetiracetm and mono-amino oxidase have been investigated.

##### Phenytoin:

Concomitant administration of eslicarbazepine acetate 1200 mg once daily and phenytoin resulted in an average decrease of 31-33% in exposure to the active metabolite, eslicarbazepine, most likely caused by an induction of glucuronidation, and an average increase of 31-35% in exposure to phenytoin, most likely caused by an inhibition of CYP2C19. Based on individual response, the dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased.

##### Digoxin:

Concomitant administration of eslicarbazepine acetate had no relevant effect on the extent of systemic exposure to digoxin. With respect to the rate of systemic exposure, concomitant administration of eslicarbazepine acetate decreased  $C_{max}$  of digoxin by 15%, which is not expected to affect the therapeutic efficacy. Safety should not be affected negatively [9].

##### Warfarin:

Co-administration of eslicarbazepine acetate 1200 mg once daily with warfarin showed a significant decrease in exposure to S-warfarin, with no significant effect on the R-warfarin pharmacokinetics; since S-warfarin clearance is mediated almost entirely by CYP2C9, whereas R-warfarin clearance is dependent on multiple CYP pathways (CYP2C19, CYP3A4 and CYP1A2) [9].

##### Lamotrigine:

There is no significant pharmacokinetic interaction between eslicarbazepine acetate and lamotrigine in healthy subjects. Therefore, no dosage adjustment appears to be usually required in either lamotrigine or eslicarbazepine acetate when the drugs are co-administered [10].

**Topiramate:**

Concomitant administration of eslicarbazepine acetate 1200 mg once daily and topiramate 200 mg once daily showed no significant change in exposure to eslicarbazepine but an 18% decrease in exposure to topiramate, most likely caused by a reduced bioavailability of topiramate. No dose adjustment is required<sup>[11]</sup>.

**Oral contraceptives:**

Eslicarbazepine acetate adversely interacts with oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped. Administration of eslicarbazepine acetate to female subjects showed a decrease in systemic exposure to both hormones of a combined oral contraceptive containing levonorgestrel and ethinylloestradiol. Therefore, it must be considered that concurrent use of eslicarbazepine acetate and hormonal contraceptives may render the contraceptives less effective<sup>[5]</sup>.

**Carbamazepine, valproate and levetiracetam:**

Concomitant treatment with carbamazepine increased the risk of the following adverse reactions: diplopia, abnormal coordination, and dizziness. The risk of increase of other specific adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded.

Monoamino Oxidase Inhibitors (MAOIs):

Based on a structural relationship of eslicarbazepine acetate to tricyclic antidepressants, an interaction between eslicarbazepine acetate and MAOIs is theoretically possible<sup>[9]</sup>.

**Pregnancy and lactation:**

There are no data from the use of eslicarbazepine acetate in pregnant women. If women receiving eslicarbazepine acetate become pregnant or plan to become pregnant, the use of eslicarbazepine acetate should be carefully re-evaluated. Minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy.

It is unknown whether eslicarbazepine acetate is excreted in human breast milk. Animal studies have shown excretion of eslicarbazepine in breast milk. As a risk to the breast-fed child cannot be excluded breastfeeding should be discontinued during treatment with eslicarbazepine acetate.

Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy<sup>[9]</sup>.

**Safety related to drug-drug interactions and other interactions:**

Although the incidence of treatment-emergent adverse events (TEAEs) is higher in subjects treated with concomitant carbamazepine than in subjects not treated with carbamazepine, this is true for both eslicarbazepine acetate and placebo treated subjects.

Diplopia is reported more frequently by patients taking eslicarbazepine acetate plus carbamazepine compared to the overall population<sup>[5]</sup>.

**Contraindications:**

Hypersensitivity to the active substance, to other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or to any of the excipients. Known to cause second or third degree atrioventricular (AV) block<sup>[6]</sup>.

**Special precautions:**

- Eslicarbazepine acetate has been associated with some central nervous system adverse reactions, such as dizziness and somnolence, which could increase the occurrence of accidental injury.

- Eslicarbazepine acetate may decrease the effectiveness of hormonal contraceptives. Additional non hormonal forms of contraception are recommended when using eslicarbazepine acetate. As with other anti-epileptic medicinal products, if Zebinix is to be discontinued it is recommended to withdraw it gradually to minimise the potential of increased seizure frequency.

- Concomitant use of eslicarbazepine acetate with oxcarbazepine is not recommended because this may cause overexposure to the active metabolites.

- Hyponatraemia has been reported as an adverse reaction in less than 1% of patients treated with eslicarbazepine acetate. Hyponatraemia is asymptomatic in most cases, however, it may be accompanied by clinical symptoms like worsening of seizures, confusion, decreased consciousness. Frequency of hyponatraemia increased with increasing eslicarbazepine acetate dose. In patients with pre-existing renal disease leading to hyponatraemia, or in patients concomitantly treated with medicinal products which may themselves lead to hyponatraemia (e.g. diuretics, desmopressin), serum sodium levels should be examined before and during treatment with eslicarbazepine acetate. Furthermore, serum sodium levels should be determined if clinical signs of hyponatraemia occur. Apart from this, sodium levels should be determined during routine laboratory examination. If clinically relevant hyponatraemia develops, eslicarbazepine acetate should be discontinued.

- Prolongations in PR interval have been observed in clinical studies with eslicarbazepine acetate. Caution should be exercised in patients with medical conditions (e.g. low levels of thyroxine, cardiac conduction abnormalities), or when taking concomitant medicinal products known to be associated with PR prolongation.

As clinical data are limited in patients with mild to moderate hepatic impairment and pharmacokinetic and clinical data are missing in patients with severe hepatic impairment, Zebinix should be used with caution in patients with mild to moderate hepatic impairment and is not recommended in patients with severe hepatic impairment.

- Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic active substances in several indications. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for eslicarbazepine acetate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered<sup>[5]</sup>.

**Clinical trials:**

Eslicarbazepine has undergone extensive clinical trials, being used alone or in combination with carbamazepine, valproic acid and lamotrigine by several groups of researchers over different time periods with various doses. Such trial results were found to be highly encouraging for therapeutic use of the compound in partial-onset seizure either alone or as an adjunct to refractory seizures with tolerable side effects<sup>[12]</sup>.

Administering eslicarbazepine acetate once-daily at doses of 800 mg and 1200 mg results in significant reduction in the frequency of partial seizures in patients over each 12-week

maintenance period versus placebo. Furthermore, patients treated with eslicarbazepine acetate demonstrated sustained reduction in seizures over an open-label, one-year period, and eslicarbazepine acetate was generally well tolerated. Patients administered eslicarbazepine acetate also demonstrated statistically significant improvements in mean quality of life as measured by Quality of Life [13, 14].

The three Phase III, multi-center, randomized, double-blinded, placebo-controlled trials involved more than 1,000 patients from 23 countries. Patients had a history of at least four partial seizures per month despite treatment with up to three concomitant anti-epileptic drugs.

During the trials, patients were randomized to eslicarbazepine acetate or placebo and after a 2-week titration period, were assessed over a 12-week maintenance period, with continued follow-up over a one-year, open-label period [15].

#### **Therapeutic drug monitoring:**

As eslicarbazepine acetate is a prodrug almost instantaneously converted to S-licarbazepine (S-Lic; approximately 95%), therapeutic drug monitoring is suggested to assess the potential interference of carbamazepine or its metabolites in the enantioselective therapeutic drug monitoring of eslicarbazepine acetate (using S-Lic concentrations). It is also useful for therapeutic drug monitoring programs in which switching from carbamazepine to eslicarbazepine acetate is implemented [16].

#### **Advantages over carbamazepine and oxcarbazepine:**

Eslicarbazepine acetate appears to have a more favorable profile than its relative's carbamazepine and oxcarbazepine. With a once-daily dosing schedule, it appears to have the efficacy features but not the adverse side effects that so often plague patients taking oxcarbazepine and carbamazepine. In retrospective analysis over a 5-year period, hyponatremia (<125 mmol/L) has been found in 9.2% of the patients taking oxcarbazepine. Hyponatremia occurred rarely with eslicarbazepine acetate. In addition, the rate of rash incidences was very low, even when eslicarbazepine acetate was taken concomitantly with carbamazepine. In the SANAD study, which evaluated the efficacy and tolerability of monotherapy drugs for patients with new onset epilepsy, the rash rate for oxcarbazepine is 6% and 7% for carbamazepine. The reduced rates of rash and hyponatremia associated with eslicarbazepine acetate will benefit patients, especially given that carbamazepine and oxcarbazepine are currently considered the gold standard drugs to treat partial seizures [17].

Cognitive and psychiatric side effects associated with eslicarbazepine acetate are very few, which is also a leap forward in treatment of patients with epilepsy [18].

#### **Quality of life measures:**

Eslicarbazepine acetate studies also improved scores of health related quality of life measures such as reduced 'seizure worry', improvements in 'cognitive functioning' and reduced 'medication effects', all factors which significantly affect the lives of patients living with epilepsy.

It has been evaluated the quality of life and the symptoms of depression during long-term treatment with eslicarbazepine acetate, given as adjuvant therapy in patients with refractory partial-onset epilepsy. All patients on trial were evaluated using the Quality-of-Life in Epilepsy Inventory-31 (QOLIE-31) and the Montgomery-Asberg Depression Rating Scale (MADRS) at baseline (prior to randomisation) and at the end of the open-label treatment [19].

#### **Effect of age:**

Eslicarbazepine acetate is shown to be extensively metabolized to eslicarbazepine (Slicarbazepine) and, in a minor extent, to R-licarbazepine. Eslicarbazepine represented between 95% and 98% of total systemic drug exposure (as assessed by AUC, ie, AUC over the dosing interval) and therefore is expected to be mainly responsible for pharmacological activity following administration of eslicarbazepine acetate. With multiple dosing, steady state plasma concentrations are attained at 4 to 5 days of administration in both age groups, consistent with an effective half-life on the order of 17 to 18 hours. In conclusion, the pharmacokinetics of Eslicarbazepine acetate is essentially similar in elderly and young patients [18].

#### **Regulatory approvals:**

EC has approved once daily dose of eslicarbazepine acetate (Zebinix) as add-on (adjunctive) therapy in adults with partial-onset seizures, with or without secondary generalisation.

#### **Conclusions:**

Eslicarbazepine acetate, administered once-daily, demonstrated to be very efficacious in partial epilepsy refractory patients, a characteristic that may relate to the preferential metabolism into S-licarbazepine, escaping drug efflux transporters, such as P-gp and MRP. It has been observed that approximately 25% became seizure free 1 month after initiation of eslicarbazepine acetate therapy [17].

Eslicarbazepine may not only be used as an add-on drug for refractory patients with partial onset seizures but may in some cases replace carbamazepine and oxcarbazepine in less the severely affected population, affording patients easier use and fewer side effects, while enjoying the same or better efficacy. Naturally, more clinical trial results are necessary in order to determine the value of eslicarbazepine and to establish just how effective and useful this drug will be in the clinic [10]. As add-on therapy, phase III clinical trials of eslicarbazepine acetate (ESL) conducted in patients with refractory partial-onset seizures have shown good efficacy, safety, and tolerability, even in patients taking carbamazepine (CBZ) at baseline (approximately 60% of the enrolled patients). Thus, considering the pharmacological disadvantages of carbamazepine and the similar efficacy spectrum of carbamazepine and eslicarbazepine acetate, switching to eslicarbazepine acetate may be successful in many patients [16].

From the above observations it can be concluded that eslicarbazepine acetate is an ideal adjunct to carbamazepine and oxcarbazepine in partial onset seizures with or without generalisation because of its molecular variation results in differences in metabolism, preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide.

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