

Brand Name: Aptiom

Generic Name: eslicarbazepine

Manufacturer: Sunovion Pharmaceuticals Inc¹

Product Availability: FDA approved November 2013. Anticipated availability is late 2014.²

Drug Class: Anticonvulsant, central nervous system agent, voltage-gated sodium channel blocker^{3,4}

Uses:

- Labeled uses: Adjunctive treatment of partial seizures^{3,4}
- Unlabeled uses: None
 - Under investigation for use as monotherapy for treatment of focal epilepsy or partial-onset seizures⁵
 - Under investigation as a possible treatment for bipolar disorder^{3,5,6}

Mechanism of Action:

Like many other anticonvulsants, the exact mechanism of action of eslicarbazepine is unknown. The antiepileptic action of the drug is theorized to be due to the blockage of voltage-gated sodium channels. Studies indicate that eslicarbazepine and its metabolites competitively interact with voltage-gated sodium channels to inhibit sustained repetitive neuronal firing, with enhanced inhibitory selectivity for rapidly firing neurons.^{1,3}

Pharmacokinetics:

- **Absorption:** ^{1,3}

T_{max}	1-4 hours
V_d	61 L
t_½	13-20 hours
Clearance	20 mL/min
GFR	80-120 mL/min
Protein binding	< 40% (% to albumin unknown)
Bioavailability	> 90%

- **Metabolism:** ^{1,3}

Eslicarbazepine is rapidly metabolized to its major active metabolite eslicarbazepine (91%) by hydrolytic first-pass metabolism. Minor active metabolites are R-licarbazepine (5%) and oxcarbazepine (1%).

In *in vitro* studies, eslicarbazepine acetate was found to be a moderate inhibitor of CYP2C19 and an inducer of CYP3A4. Studies with eslicarbazepine in fresh human hepatocytes showed only mild activation of UGT1A1- mediated glucuronidation.

Eslicarbazepine showed no clinical inhibitory effects on CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4 and did not undergo autoinduction.

- **Elimination:** ^{1,3}

Eslicarbazepine metabolites are eliminated primarily by renal excretion in the unchanged and glucuronide conjugate forms. Eslicarbazepine and its glucuronide make up a total of 90% of metabolites excreted in urine with minor metabolites accounting for 10%. The renal clearance of eslicarbazepine in healthy subjects is substantially lower than the glomerular filtration rate (20 mL/min compared to 80-120 mL/min), indicating that renal tubular reabsorption occurs.

Efficacy:

Elger C, Halász P, Maia J, Almeida L, Soares-da-Silva P. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. *Epilepsia*. 2009 Mar;50(3):454-63.⁸

Study Design: double-blind, randomized, placebo-controlled, parallel-group, multicenter, Phase III study

Description of Study: *Objective:* study the efficacy and safety of eslicarbazepine acetate (ESL) as adjunctive therapy for refractory partial seizures in adults with ≥ 4 partial-onset seizures (simple or complex, with or without secondary generalization) per 4 weeks despite treatment with 1-2 antiepileptic drugs (AEDs). *Methods:* This multicenter, parallel-group study had an 8-week, single-blind, placebo baseline phase, after which patients were randomized to placebo (n = 102) or once-daily ESL 400 mg (n = 100), 800 mg (n = 98), or 1,200 mg (n = 102) in the double-blind treatment phase. ESL starting dose was 400 mg; thereafter, ESL was titrated at weekly 400-mg steps to the full maintenance dose (12 weeks). Efficacy data were documented by means of diaries. The frequency and types of seizures were determined based on the entries from these diaries. *Results:* Seizure frequency adjusted per 4 weeks over the maintenance period (primary endpoint) was significantly lower than placebo in the ESL 1,200 mg (p = 0.0003) and 800 mg (p = 0.0028) groups. Responder rate was 20% (placebo), 23% (400 mg), 34% (800 mg), and 43%

(1,200 mg). Median relative reduction in seizure frequency was 16% (placebo), 26% (400 mg), 36% (800 mg), and 45% (1,200 mg). Similar efficacy results were obtained in patients administered ESL with or without carbamazepine as concomitant AED. Discontinuation rates caused by adverse events (AEs) were 3.9% (placebo), 4% (400 mg), 8.2% (800 mg), and 19.6% (1,200 mg). AEs in >10% of any group were dizziness, headache, and diplopia. Most AEs were mild or moderate.

Limitations: Data was documented from patient diaries, including seizure type. This could potentially lead to incorrectly recorded frequency and seizure type. The study did not include a statistical test for demographics or adverse events. Also, adherence was not assessed.

Conclusion: ESL, 800 and 1,200 mg once-daily, was well tolerated and more effective than placebo in patients who were refractory to treatment with one or two concomitant AEDs.

Ben-Menachem E, Gabbai AA, Hufnagel A, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. *Epilepsy Res.* 2010 May;89(2-3):278-85.⁹

Study Design: Double-blind, randomized, placebo-controlled, parallel-group, multicenter, Phase III study

Description of Study: *Objective:* evaluate efficacy and safety of once-daily eslicarbazepine acetate (ESL) when used as add-on treatment in adults with ≥ 4 partial-onset seizures per 4-week despite treatment with 1 to 3 antiepileptic drugs (AEDs). *Methods:* 503 Patients entered an observational 8-week baseline phase (during which they continued to receive standard AEDs) to establish pretreatment seizure frequency. At the start of the double-blind phase (14-week treatment), patients were randomized in a 1:1:1:1 ratio to one of the following 4 treatment groups: placebo, ESL 400 mg, 800 mg, or 1200 mg once-daily. All patients started at their full maintenance dose except for those in the ESL 1200 mg group, who started at 800 mg once-daily for a 2-week titration period before reaching the full maintenance dose. Efficacy data were documented through patient diaries. Seizure frequency was the primary efficacy variable, which was evaluated based on diary entries. Safety data included adverse events (AEs). *Results:* Seizure frequency per 4-week (primary endpoint) over the 14-week double-blind treatment period was significantly lower than placebo in the ESL 800 mg and 1200 mg ($p < 0.001$) groups. Responder rate ($\geq 50\%$ reduction in seizure frequency) was 13.0% (placebo), 16.7% (400 mg), 40.0% (800 mg, $p < 0.001$), and 37.1% (1200 mg, $p < 0.001$). Median relative reduction in seizure frequency was 0.8% (placebo), 18.7% (400 mg), 32.6% (800 mg, $p < 0.001$), and 32.8% (1200 mg). Discontinuation rates due to adverse events (AEs) were 3.0% (placebo), 12.5% (400 mg), 18.8% (800 mg), and 26.5% (1200 mg). The most common ($>5\%$) AEs in any group were dizziness, somnolence, headache, nausea, diplopia, abnormal coordination, vomiting, blurred vision, and fatigue. The majority of AEs were of mild or moderate severity.

Limitations: Data was documented from patient diaries, including seizure type. This could potentially lead to incorrectly recorded frequency and seizure type. The study did not include a statistical test for demographics or adverse events. Also, adherence was not assessed.

Conclusions: Treatment with once-daily eslicarbazepine acetate 800 mg and 1200 mg was more effective than placebo in patients with partial-onset seizures refractory to treatment with 1 to 3 concomitant AEDs in this study. However, higher doses had a large discontinuation rate due to adverse events.

Hufnagel A, Ben-Menachem E, Gabbai AA, Falcão A, Almeida L, Soares-da-Silva P. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: results of a 1-year open-label extension study. *Epilepsy Res.* 2013 Feb;103(2-3):262-9.¹⁰

Study Design: open-label extension study of patients who completed a randomized, double-blind placebo-controlled trial

Description of Study: *Objective:* evaluate the long-term safety, tolerability and efficacy of once-daily eslicarbazepine acetate (ESL) as adjunctive therapy in adults with partial-onset seizures. *Methods:* One-year open-label extension (OLE) study with ESL in patients who completed a randomized, double-blind placebo-controlled trial (*Epilepsy Res.* 89 (2010) 278-285). Starting dose was 800 mg once-daily, for 4 weeks; thereafter, dose could be individualized within the 400-1,200 mg range. Doses of concomitant antiepileptic drugs were to be kept stable. The efficacy assessments were based on patient diaries. Other outcome measures included quality of life and depressive symptoms. *Results:* Overall, 325 patients were enrolled and 223 (68.6%) patients completed 1-year of treatment. ESL median dose was 800 mg once-daily. Compared to the baseline period of the double-blind study completed prior to this OLE study, median seizure frequency decreased by 32% in weeks 1-4, and between 37% and 39% thereafter. The responder rate (seizure reduction \geq 50%) was 37% during weeks 1-4 and thereafter ranged between 38% and 42% per 12-week interval. Proportion of seizure-free patients per 12-week interval ranged between 5% and 11%. Improvements from baseline in several Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and Montgomery Asberg Depression Rating Scale (MADRS) scores were observed. Adverse events (AEs) were reported by 83% of patients. AEs occurring in \geq 10% of patients were dizziness, headache and somnolence. AEs were usually of mild to moderate intensity.

Limitations: Data was documented from patient diaries, including seizure type. This could potentially lead to incorrectly recorded frequency and seizure type. The study did not include a statistical test for demographics or adverse events. Also, adherence was not assessed.

Conclusions: In this study, ESL demonstrated a sustained therapeutic effect during 1-year add-on treatment of adults with partial-onset seizures. Additionally, significant improvements in

quality of life domains and depressive symptoms were observed under long-term treatment with once-daily ESL. However, a large number of adverse events were reported.

Contraindications: ^{1,3,4}

Eslicarbazepine is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

- Dermatologic reactions including Stevens-Johnson Syndrome have been reported
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Multiorgan Hypersensitivity has been reported
 - Presentation: fever, rash, lymphadenopathy, other organ system involvement, eosinophilia
 - Report fever or lymphadenopathy immediately, rash may not be evident
 - Drug should be discontinued and not resumed if alternative etiology for symptoms cannot be established
- Anaphylactic reactions and angioedema rarely reported

Precautions: ^{1,3,4}

- Suicidal behavior and ideation: Antiepileptic drugs, increase the risk of suicidal thoughts or behavior in patients taking these medications for any indication. Patients treated with any antiepileptic drug should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Hyponatremia: Clinically significant hyponatremia (Na <125 mEq/L) can develop in patients taking eslicarbazepine. Life-threatening complications were reported including seizures, severe nausea/vomiting, severe gait instability, and injury. Depending on severity, eslicarbazepine may need to be reduced or discontinued. Measurement of serum sodium and chloride levels should be considered during maintenance treatment and should be performed if symptoms of hyponatremia develop.
- Neurological adverse reactions: dizziness and disturbance in gait and coordination, somnolence and fatigue, cognitive dysfunction, and visual changes have been reported. Patients should be advised to avoid operation of motor vehicles or dangerous machinery until the effect of eslicarbazepine is known.
- Withdrawal: as in all antiepileptic drugs, eslicarbazepine should be gradually tapered off due to risk of increased seizure frequency and status epilepticus.
- Drug induced liver injury: Mild-moderate elevations in transaminases (>3 times upper limit) and elevations in total bilirubin (>2 times upper limit) have been reported.

Baseline liver laboratory tests are recommended and eslicarbazepine should be discontinued in patients with jaundice or other evidence of significant liver injury.

- Abnormal thyroid function tests: Dose-dependent decreases in serum T3 and T4 values have been observed in patients taking eslicarbazepine. Changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated.

Adverse Effects (Incidence):^{1,4}

Incidence >10%:

Gastrointestinal Effects

- Nausea (10-16%)

Neurologic Effects

- Dizziness (20-28%)
- Headache (13-15%)
- Hypersomnia (16-28%)
- Lethargy (16-28%)
- Sedation (16-28%)
- Somnolence (11-18%)

Ophthalmic Effects

- Diplopia (9-11%)

Other

- Malaise (16-28%)

Incidence <10%:

Dermatologic Effects

- Rash (1-3%)
- Stevens-Johnson syndrome (<1%)

Endocrine/Metabolic Effects

- Hyponatremia (2%)

Gastrointestinal Effects

- Diarrhea (2-4%)

- Vomiting (6-10%)

Hematologic Effects

- Drug-Reaction with Eosinophilia and Systemic Symptoms (DRESS) (<1%)

Immunologic Effects

- Anaphylaxis (<1%)

Neurologic Effects

- Abnormal gait (2%)
- Amnesia (4-7%)
- Aphasia (4-7%)
- Asthenia (2-3%)
- Ataxia (4-6%)
- Confusion (4-7%)
- Disorientation (4-7%)
- Disturbance in speech (4-7%)
- Disturbance of attention (4-7%)
- Dysarthria (1-2%)
- Impairment of balance (3%)
- Insomnia (2%)
- Memory impairment (1-2%)
- Motor retardation (4-7%)
- Slow flow of thought (4-7%)
- Tremor (2-4%)
- Vertigo (2-6%)

Ophthalmic Effects

- Blurred vision (5-6%)
- Nystagmus (1-2%)
- Visual impairment (1-2%)

Psychiatric Effects

- Depression: (1-3%)
- Suicidal thoughts: (<1%)

Other

- Angioedema (<1%)
- Falls (1-3%)

- Fatigue (4-7%)

Drug Interactions: ^{1,4}

CYP3A4 substrates:

Eslicarbazepine is a CYP3A4 inducer and may decrease the exposure of CYP3A4 substrates. If used concomitantly, use caution and monitor the patient closely.

- Medications: abiraterone, ado-trastuzumab, alfentanil, alprazolam, amiodarone, amlodipine, apixaban, aprepitant, aripiprazole, astemizole, atazanavir, atorvastatin, bedaquiline, boceprevir, bosutinib, brentuximab, brinzolamide, bromocriptine, budesonide, buprenorphine, buspirone, cabazitaxel, cabozantinib, cilostazol, cilostazol, citalopram, clarithromycin, clozapine, cyclosporine, dabrafenib, darifenacin, darunavir, dasatinib, delavirdine, dexamethasone, dihydroergotamine, docetaxel, dronedarone, dutasteride, eletriptan, eplerenone, ergotamine, erythromycin, escitalopram, estradiol, felodipine, fentanyl, fluticasone, haloperidol, hydrocodone, imatinib, indinavir, itraconazole, ivabradine, ketoconazole, letrozole, losartan, lovastatin, lurasidone, maraviroc, medroxyprogesterone, methadone, midazolam, nateglinide, nelfinavir, nifedipine, nilotinib, ondansetron, oxycodone, paclitaxel, prednisolone, prednisone, quetiapine, quinidine, ranolazine, rifabutin, ritonavir, salmeterol, saxagliptin, sildenafil, tacrolimus, tamoxifen, tamsulosin, ticagrelor, tramadol, trazodone, triamcinolone, verapamil, zileuton, zolpidem

CYP2C19 substrates:

Eslicarbazepine is a CYP2C19 inhibitor and may increase the exposure of CYP2C19 substrates. If used concomitantly, use caution and monitor the patient closely.

- Medications: amitriptyline, carisoprodol, citalopram, clobazam, clomipramine, clopidogrel, cyclophosphamide, diazepam, doxepin, escitalopram, esomeprazole, lansoprazole, mephenytoin, meprobamate, nelfinavir, omeprazole, pantoprazole, progesterone, propranolol

Carbamazepine:

If eslicarbazepine acetate and carbamazepine are administered concomitantly, the dose of eslicarbazepine acetate or carbamazepine may need to be adjusted based on efficacy and tolerability. The concomitant administration of eslicarbazepine acetate and carbamazepine decreases the exposure of the active metabolite, eslicarbazepine, by approximately 32%. The combination also increased the incidence of diplopia and dizziness compared with administration of eslicarbazepine alone.

Ethinyl estradiol/levonorgestrel:

Concurrent administration of eslicarbazepine and hormonal oral contraceptives containing ethinyl estradiol and levonorgestrel may decrease the exposure of the oral contraceptive. Women using hormonal oral contraceptives should use additional or alternative non-hormonal contraception during treatment with eslicarbazepine acetate and for at least 1 menstrual cycle after treatment discontinuation of eslicarbazepine

Phenytoin/fosphenytoin:

Concomitant administration of eslicarbazepine and phenytoin decreased the exposure to eslicarbazepine and increased the exposure of phenytoin. Coadministration of eslicarbazepine, a CYP2C19 inhibitor, and phenytoin, a CYP2C19 substrate, may require an increased eslicarbazepine dose and a phenytoin dose adjustment based on clinical response and phenytoin plasma levels. Monitor plasma phenytoin concentrations during concurrent therapy.

Phenobarbital/primidone:

Concurrent administration of eslicarbazepine with enzyme-inducing antiepileptic drugs may decrease the plasma concentrations of eslicarbazepine. A higher eslicarbazepine dose may be needed when used together.

Simvastatin:

Coadministration of eslicarbazepine, a CYP3A4 inducer, with simvastatin, a CYP3A4 substrate, may reduce simvastatin plasma concentrations. If used concurrently, adjust the simvastatin dose if a clinically significant change in lipid levels occurs.

Warfarin:

Concurrent administration of eslicarbazepine with warfarin may decrease warfarin plasma concentrations. When co-administered, perform patient monitoring to maintain INR.

Dosing/Administration:^{1,2,3,4}

- **Usual Adult Dose:**
 - Start with 400 mg by mouth once daily. After 1 week, increase the dose to the recommended maintenance dosage of 800 mg by mouth once daily.
 - Treatment may be initiated at 800 mg by mouth once daily if the need for additional seizure reduction outweighs an increased risk of adverse reactions during initiation
 - The maximum recommended maintenance dosage of 1200 mg PO daily may be beneficial for some patients but is associated with increased adverse events.
 - 1200 mg/day should only be initiated after a patient has tolerated 800 mg/day for at least 1 week
 - Gradually taper off eslicarbazepine due to risk of seizures and status epilepticus

- **Geriatric Dose:**
 - Insufficient data on efficacy in geriatric patients
 - Pharmacokinetics of eslicarbazepine are not affected by age independently. However, dose selection should take in consideration the greater frequency of renal dysfunction and concomitant medical conditions in elderly patients

- **Pediatric Dose:**
 - Safety and efficacy have not been established

- **Renal Impairment Dose:**
 - CrCl \geq 50 ml/min: no adjustment needed
 - CrCl $<$ 50 ml/min: initiate therapy at 200 mg by mouth once daily. After 2 weeks, increase to the recommended maintenance dose of 400 mg by mouth once daily. Some patients may benefit from a maximum recommended maintenance dose of 600 mg by mouth once daily.

- **Hepatic Impairment Dose:**
 - No dosage adjustments recommended for mild to moderate hepatic impairment.
 - The effects of severe hepatic impairment have not been evaluated, therefore use in this population is not recommended.

Use in Special Circumstances:

- **Pregnancy:**^{1,3}
 - FDA pregnancy risk category C
 - Although there are no clinical trials documenting its effect in pregnant women, results of some animal studies indicate that eslicarbazepine may be teratogenic in humans
 - Therefore, eslicarbazepine should only be used during pregnancy if the benefits of treatment clearly outweigh the risks to the fetus

- **Lactation:**^{1,3}
 - Eslicarbazepine is excreted into breast milk
 - Because of the potential for serious adverse reactions in nursing babies, a decision should be made whether to discontinue nursing or to discontinue the drug
 - The American Academy of Pediatrics (AAP) lists related drug, carbamazepine, to be usually compatible with breast-feeding. However, the AAP has not evaluated eslicarbazepine⁷

- Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition

Conclusion:

Eslicarbazepine appears to be a safe and effective drug that can offer valid additional therapy to current first or second-line antiepileptic medications. It demonstrated a therapeutic effect as add-on treatment in adults with partial-onset seizures and sustained efficacy during a 1-year longer-term study. Additionally, significant improvements in quality of life domains and depressive symptoms were observed under long-term treatment with once-daily eslicarbazepine. However, limitations to these studies may warrant further research. The use of eslicarbazepine shows promise for refractory partial seizures in patients who need additional adjunctive therapy. However, the cost of this new, brand-only medication and drug interactions may further limit its use.

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