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ESLICARBAZEPINE ACETATE

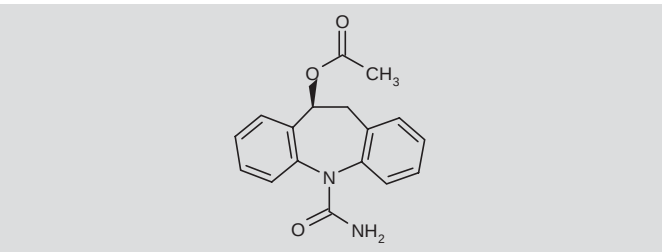
Sodium Channel Blocker
Antiepileptic Drug

Rec INNM; USAN

BIA-2-093
SEP-0002093
Exalief®
Zebinix®
Stedesa™

Acetic acid 5-carbamoyl-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-10(*S*)-yl ester

InChI=1/C17H16N2O3/c1-11(20)22-16-10-12-6-2-4-8-14(12)19(17(18)21)15-9-5-3-7-13(15)16/h2-9,16H,10H2,1H3,(H2,18,21)/t16-/m0/s1



$C_{17}H_{16}N_2O_3$
Mol wt: 296.3205
CAS: 236395-14-5
EN: 278670

ABSTRACT

Eslicarbazepine acetate (BIA-2-093) is a prodrug of eslicarbazepine ([S]-licarbazepine), a third-generation drug belonging to the carbamazepine (CBZ) family and the active metabolite of oxcarbazepine (OXC). Eslicarbazepine acetate is currently being developed as a new antiepileptic drug (AED), with the aim of improving the efficacy and tolerability profiles of CBZ and OXC. Favorable phase III data from studies in patients with partial-onset seizures have indicated effective reductions in seizure frequency, good response rates, good safety and improvements in quality-of-life parameters when eslicarbazepine acetate is used as add-on therapy. These studies have resulted in the recent recommendation by the EMEA granting marketing authorization to BIAL - Portela (Zebinix®, Exalief®; to be marketed in Europe by Eisai). Clinical development of eslicarbazepine acetate (Stedesa™) is also under way in the U.S. and Canada by licensee Sepracor.

SYNTHESIS

Eslicarbazepine acetate can be prepared by several related ways:

Reduction of oxcarbazepine (I) using $NaBH_4$ in ethanol/water yields the racemic alcohol (II), which is resolved into its enantiomers by means of fractional crystallization of the diastereomeric esters obtained from alcohol (II) and menthoxyacetyl chloride (III). Alkaline hydrolysis of the desired diastereoisomer (IV) provides the (*S*)-alcohol (V) (1, 2), which is finally acylated with acetyl chloride and DMAP in pyridine/CH_2Cl_2 (1-4). Scheme 1.

Condensation of racemic alcohol (II) with di-*O*-acetyl-L-tartaric acid anhydride (VI) – obtained by treatment of L-tartaric (VII) acid with hot AcO_2 and trace H_2SO_4 – gives a disastereomeric mixture of tartrate monoesters (VIII), which is separated into diastereomeric alcohol esters by fractional crystallization in water and then the desired (*S*)-diastereomer hydrolyzed under alkaline conditions to afford alcohol (V) (3). Scheme 1.

Alcohol (V) can also be obtained by enantioselective reduction of oxcarbazepine (I) by transfer hydrogenation with formic acid/triethylamine in the presence of the chiral Noyori catalyst [(*S,S*)-*N*-tosyl-1,2-diphenylethylenediamino](η^6-*p*-cymene)chlororuthenium (4, 5). Scheme 2.

Alternatively, treatment of oxcarbazepine (I) with acetic anhydride and DMAP in pyridine/CH_2Cl_2 yields the enol acetate (IX), which is submitted to asymmetric hydrogenation with H_2 in the presence of a chiral rhodium(I) catalyst (6). Scheme 2.

In all the synthetic routes, the (*R*)-enantiomer of alcohol (V) can be recycled by racemization (7) or chiral inversion (8) and reintroduced in the appropriate step.

BACKGROUND

Epilepsy is a serious health condition that is associated with a high economic burden. A review of the impact of epilepsy on the European economy in 2004 estimated a prevalence of 4.3-7.8 per 1,000, with an estimated total cost (direct costs [medical] and indirect costs [lost or reduced earnings and productivity]) of €15.5 billion (9). A 2009 report from the Centers for Disease Control and Prevention (CDC)

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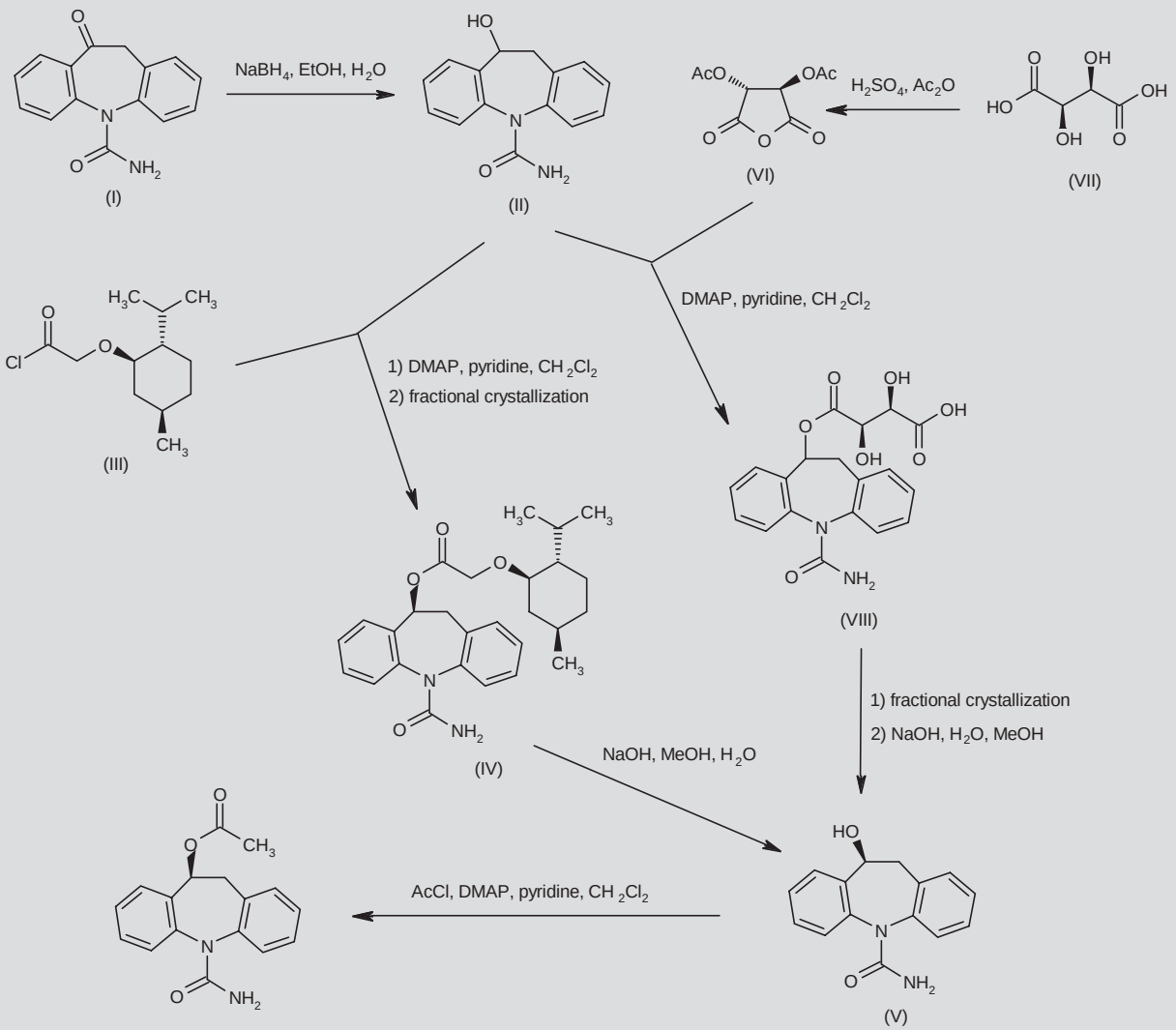
Scheme 1. Synthesis of Eslicarbazepine Acetate

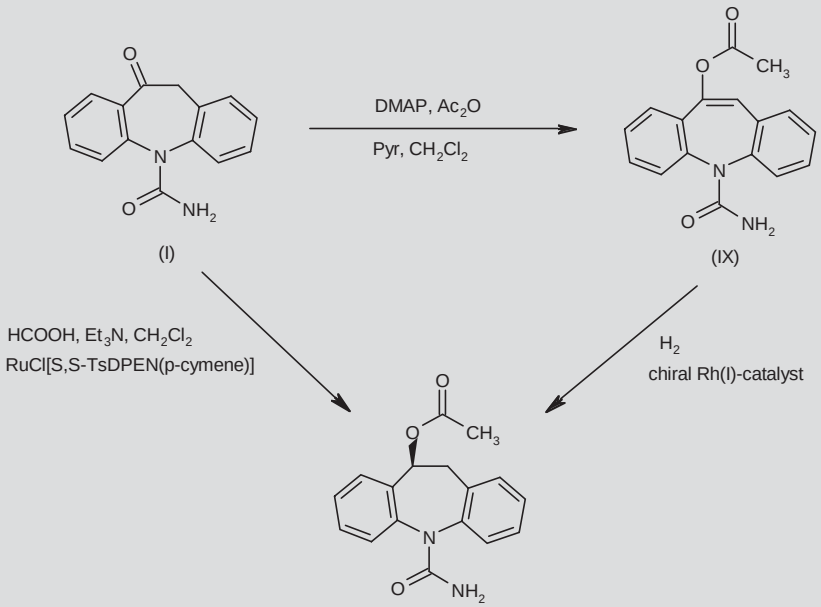


estimated that epilepsy affects 2.5 million people in the United States and accounts for $15.5 billion in total costs each year, with the daunting prospect that approximately 200,000 new cases of epilepsy are diagnosed each year in the U.S. (10). Pharmacoresistance remains a key issue surrounding the substantial cost of epilepsy and greatly increases a person's risk for subsequent seizures, brain damage, disability and death from injuries incurred during a seizure (11).

Carbamazepine (CBZ) has been the leading antiepileptic drug (AED) since the 1960s (12) and researchers have undertaken chemical modification of this sodium channel blocker to improve antiepileptic properties. The subsequent introduction of oxcarbazepine (OXC) provided equivalent efficacy with improved tolerability (13).

A new candidate AED is eslicarbazepine acetate (BIA-2-093), a prodrug of eslicarbazepine ([*S*]-licarbazepine, structure [V] in Scheme 1), a third-generation drug belonging to the CBZ family and the active metabolite of OXC (structure [I] in Scheme 1). Eslicarbazepine acetate is a novel voltage-gated sodium channel blocker that has been shown to reduce the frequency of partial-onset seizures when used in combination with other AEDs. The European Medicines Agency (EMEA) recently recommended that marketing authorization be granted for the drug in the European Union under the names Exalief® and Zebinix® (400-, 600- and 800-mg tablets) as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization (14); it will be marketed in Europe by Eisai under license from Bial-Portela. Sepracor acquired the rights to commercialize the drug for the U.S. and Canadian markets and just recently submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval as Stedesa™ (15). Sepracor is also about to initiate a phase III trial for eslicarbazepine

Scheme 2. Synthesis of Eslicarbazepine Acetate



acetate as monotherapy in subjects with partial epilepsy not well controlled by current AEDs (16).

PRECLINICAL PHARMACOLOGY

In preliminary studies, the ability of eslicarbazepine acetate to block voltage-gated sodium channels was assessed by displacement of [^{3}H]-batrachotoxinin A 20α-benzoate (BTX) binding in rat cortical synaptosomes. Eslicarbazepine acetate demonstrated a significantly improved IC_{50} versus CBZ (138 µM vs. 210 µM) and showed significantly greater inhibition of $^{22}Na^+$ uptake compared to CBZ at concentrations of 30, 100 and 300 µM (52.6%, 73.4% and 95.6% inhibition, respectively, vs. 22.6%, 44.3% and 64.8% inhibition, respectively) (2).

Further electrophysiological assessments of the inhibitory potency of eslicarbazepine acetate on sodium currents in mouse neuroblastoma cells were subsequently carried out compared to CBZ. Like CBZ, the inhibitory potency of eslicarbazepine acetate increased as the holding potential was made less negative (–100, –90, –80 and –70 mV), with median IC_{50} values of 4337, 618, 238 and 139 µM, respectively (vs. 1506, 594, 194 and 101 µM, respectively, for CBZ). Similar potencies were also seen for the two agents for the displacement of [^{3}H]-BTX (IC_{50} = 222 and 361 µM, respectively, for eslicarbazepine acetate and CBZ) and inhibition of the uptake of $^{22}Na^+$ (IC_{50} = 36 and 138 µM, respectively). Both drugs failed to displace [^{3}H]-saxitoxin at concentrations up to 300 µM. These observations indicate that eslicarbazepine acetate inhibits sodium currents in a voltage-dependent manner predominantly via a competitive interaction with the inactivated sodium channel. This suggests that the anticonvulsant properties of eslicarbazepine acetate may be mediated via selective inhibition of rapidly firing neurons (17).

Studies in rat striatal slices also support these observations, showing that eslicarbazepine acetate inhibits veratridine-induced release of glutamate, aspartate, GABA and dopamine in a concentration-dependent manner (30-300 µM), with potency similar to CBZ and OXC (18, 19).

Investigations using the MTT assay in cultured rat hippocampal neurons indicated that eslicarbazepine acetate does not cause toxicity at 50-100 µM, whereas neurotoxicity was evident in the presence of CBZ and OXC. Markers of apoptosis (nuclear chromatin condensation and caspase-3-like enzymes) were also significantly elevated in CBZ- and OXC-treated neurons, but not in neurons exposed to eslicarbazepine acetate. On the other hand, all three compounds were found to protect hippocampal neurons from toxicity caused by kainate, veratridine or ischemia-like conditions (20).

Further histochemical studies have also shown that degeneration and swelling of neurites (as shown by the neuronal marker MAP-2) are evident in hippocampal neurons treated for 24 h with CBZ or OXC (300 µM), but not following exposure to eslicarbazepine acetate. Reactive oxygen species (ROS) were not evident in neurons treated with eslicarbazepine acetate or CBZ, but were elevated in neurons exposed to OXC. OXC was also associated with significantly decreased ATP levels and reduced mitochondrial membrane potential (21).

Initial testing against maximal electroshock (MES)-induced seizures in rats revealed that eslicarbazepine acetate provides anticonvulsant activity comparable to CBZ and superior to OXC following oral administration (ED_{50} = 4.7, 5.4 and 10.0 mg/kg, respectively), and activity comparable to OXC and somewhat lower than that of CBZ following i.p. administration (ED_{50} = 6.3, 3.4 and 6.1 mg/kg, respec-

tively). Motor impairment was evaluated in the rotarod test, indicating superiority for eslicarbazepine acetate compared to CBZ following both oral and i.p. administration (TD_{50} = 358.7 and 251.0 mg/kg p.o., respectively, and 78.6 and 27.4 mg/kg i.p., respectively), but superiority compared to OXC only following i.p. administration (TD_{50} = 40.1 mg/kg i.p., TD_{50} > 1000 mg/kg p.o.) (2).

More recent studies have investigated the anticonvulsant effect of orally administered eslicarbazepine acetate on seizures induced by picrotoxin microperfusion in the hippocampus of freely moving rats. Pretreatment with a dose of 30 mg/kg p.o. 2 h before picrotoxin prevented seizures in 75% of rats. Furthermore, no adverse effects were observed at this dose in the behavioral/EEG patterns studied, including sleep/wakefulness cycles (22, 23).

Eslicarbazepine acetate has also been shown to retard kindling epileptogenesis induced by twice-daily bilateral corneal stimulation in NMRI mice. Administration of eslicarbazepine acetate at a dose of 100 mg/kg i.p. 15 min prior to stimulation significantly reduced kindling progression (24).

PHARMACOKINETICS AND METABOLISM

In vitro and in vivo studies have shown that eslicarbazepine acetate is rapidly and extensively metabolized to eslicarbazepine ([*S*]-licarbazepine), which is then oxidized to OXC to a small extent. These events occur to approximately the same extent in human liver and intestinal microsomes, indicating significant first-pass hydrolysis (25, 26).

Tissue distribution studies in CD-1 mice have shown that following a single oral dose of eslicarbazepine acetate (350 mg/kg), brain exposure to the metabolites (*S*)-licarbazepine and OXC is approximately 30% of total systemic exposure, although (*S*)-licarbazepine appears to cross the blood–brain barrier less efficiently than OXC. On the other hand, the liver/plasma ratios suggest that (*S*)-licarbazepine undergoes hepatic accumulation, whereas OXC is cleared twice as fast as (*S*)-licarbazepine. No eslicarbazepine acetate or (*R*)-licarbazepine was detected (27).

The bioequivalence of three formulations of eslicarbazepine acetate (oral suspension of 50 mg/mL and tablets of 200 and 800 mg) was tested in a single-center, open-label, randomized, 3-way crossover study in 18 healthy subjects. No significant difference was seen among the $AUC_{0-\infty}$ and C_{max} values for these formulations, suggesting equivalent bioavailability (28, 29).

The pharmacokinetics of eslicarbazepine acetate following doses of 800 mg/day over 8 days were characterized in patients with moderate liver impairment (n = 8) and in subjects with normal liver function (n = 8). First-pass metabolism was slightly decreased by liver impairment, with more subjects with measurable plasma concentrations of the parent drug; however, this only represented about 0.01% of total systemic exposure. No differences were seen between the groups in the pharmacokinetics of the parent drug and metabolites. This study indicates that patients with mild to moderate liver impairment treated with eslicarbazepine acetate are unlikely to need dose adjustment (30-32).

The pharmacokinetics following a single dose of 800 mg eslicarbazepine acetate have also been characterized in subjects with normal renal function (n = 8) and in patients with mild (n = 8), moderate (n = 8) or severe renal impairment (n = 8), and patients with end-stage renal disease requiring hemodialysis (n = 8). While the C_{max} did not differ significantly among groups, the extent of systemic exposure, assessed by AUC, increased with decreasing renal function. Furthermore, it was shown that eslicarbazepine acetate metabolites are excreted primarily via the kidneys and thus their clearance is dependent on renal function. Dose adjustment may therefore be necessary in renal-impaired patients treated with eslicarbazepine acetate (33-35).

The pharmacokinetic profile of eslicarbazepine acetate was compared in healthy young (18-40 years of age; n = 12) and elderly (> 65 years of age; n = 12) subjects. In a single-center, open-label, nonrandomized study, subjects underwent a single-dose phase (600 mg) followed by an 8-day multiple-dose phase (600 mg/day). With multiple dosing, steady-state plasma concentrations were achieved in 4-5 days in both age groups and no significant differences were seen for any pharmacokinetic parameters assessed following single or repeated dosing (36, 37). Further examination of the subjects in this study indicated that gender did not have an effect on pharmacokinetics (38-40).

The effect of food on eslicarbazepine pharmacokinetics was also examined in healthy volunteers. In a single-center, open-label, randomized, crossover study (n = 12) it was demonstrated that the pharmacokinetic profile of a single oral dose of eslicarbazepine acetate (800 mg) was not affected by a standard high-fat meal or 10 h of fasting (41).

Data from a pooled analysis of 3 phase III studies (see below) also contributed to population pharmacokinetic investigations, along with data from a substudy in 51 patients. Analyses of multiple once-daily doses (400-1200 mg/day) has shown that the pharmacokinetic profile of the major metabolite eslicarbazepine is linear and predictable (one-compartment open model with first-order absorption), independent of concomitant administration of multiple AEDs, laboratory safety parameters, age and gender (42).

Eslicarbazepine pharmacokinetics were characterized in children and adolescents with epilepsy. Open-label, once-daily administration at escalating doses given for 4-week periods with 1-week washout phases (5, 15 and 30 mg/kg/day) to patients aged 2-6 (n = 11), 7-11 (n = 8) and 12-17 years (n = 10) indicated a t_{max} of 1-3 h for eslicarbazepine across the age ranges, with dose-proportional C_{max} and AUC_{0-24} observations. Only AUC_{0-24} was age-dependent and an inverse relationship between clearance rate and age was also identified (43).

CLINICAL STUDIES

Pooled data from 1,049 patients with partial onset seizures enrolled in 3 multicenter, double-blind, randomized, placebo-controlled phase III studies have shown that once-daily doses of 800 and 1200 mg over a period of 12 weeks can significantly reduce seizure frequency compared with placebo (–36% and –46%, respectively) in patients refractory to treatment with 1-3 concomitant AEDs. The responder rate (≥ 50% decrease in seizure frequency) was also significantly higher in the eslicarbazepine acetate 800 mg (36%) and 1200 mg (44%) groups than in the placebo group (22%). Adverse

events (AEs) tended to be transient within 6 weeks of treatment, with the most common AEs in both placebo and eslicarbazepine acetate groups reported as dizziness, somnolence, headache and nausea. The majority of patients in the eslicarbazepine acetate (84.8%) and placebo (90.3%) treatment groups had AEs of mild or moderate intensity (44). Data from the individual phase III studies have also been presented (45-47).

An additional study investigated the relationship between exposure to the main metabolite eslicarbazepine and the antiepileptic efficacy of eslicarbazepine acetate in the pooled patient cohort detailed above. It was found that the antiepileptic effect of eslicarbazepine acetate, as assessed by a decrease in seizure frequency, increased with an increase in dose. The probability of being seizure-free or a responder (≥ 50% reduction in seizure frequency) increased with eslicarbazepine concentrations (48).

Long-term data have also demonstrated the efficacy and safety of eslicarbazepine acetate over a 1-year period. Of those enrolled in the long-term study following completion of one of the phase III double-blind studies highlighted above, 68.6% (n = 223) completed 1 year of treatment. At a median daily dose of 800 mg, seizure frequency decreased by up to 39% during the 52 weeks of analysis, with maximum responder rates of 42%. The proportion of seizure-free patients per 12-week intervals increased over time, from 5% at weeks 5-16 to 11% at weeks 41-52. A total of 11.4% of patients discontinued due to treatment-emergent AEs, which were of mild to moderate severity in 82% of patients (events occurring in at least 10% of patients included dizziness [27%], headache [16%] and somnolence [12%]) (49). Patients involved in this long-term study also demonstrated a statistically and clinically significant improvement in quality of life, as assessed by the Quality-of-Life in Epilepsy Inventory 31 (QOLIE-31; significant improvements vs. baseline: overall quality of life, seizure worry, medication effects and the overall score [intent-to-treat population]), and depressive mood, as assessed by the Montgomery Asberg Depression Rating Scale (MADRS; significant improvements: total score, apparent sadness, inner tension, reported sadness, reduced sleep, inability to feel, and pessimistic thoughts) (50).

DRUG INTERACTIONS

Single-center, randomized, double-blind placebo-controlled, two-way crossover studies have investigated drug–drug interactions in healthy subjects. Eslicarbazepine acetate at a dose of 1200 mg once daily was shown to have no relevant effect on steady-state systemic exposure of digoxin (51, 52), metformin (53) or lamotrigine (54).

SOURCES

Bial-Portela (PT); licensed to Eisai for Europe and to Sepracor for the U.S. and Canada.

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