PRODUCT MONOGRAPH

Pr APTIOM®

eslicarbazepine acetate

200 mg, 400 mg, 600 mg and 800 mg Tablets

Professed

Antiepileptic

Sunovion Pharmaceuticals Canada Inc.
6790 Century Ave., Suite 100
Mississauga, Ontario
Canada

Date of Preparation:
June 27, 2018

Submission Control No: 208086

Under license from Bial

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 12
DRUG INTERACTIONS 15
DOSAGE AND ADMINISTRATION 18
OVERDOSAGE 19
ACTION AND CLINICAL PHARMACOLOGY 19
STORAGE AND STABILITY 22
DOSAGE FORMS, COMPOSITION AND PACKAGING 23

PART II: SCIENTIFIC INFORMATION 24
PHARMACEUTICAL INFORMATION 24
CLINICAL TRIALS 25
DETAILED PHARMACOLOGY 28
TOXICOLOGY 30
REFERENCES 35

PART III: PATIENT MEDICATION INFORMATION 36

[Pr]APTIOM®

eslicarbazepine acetate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets / 200 mg, 400 mg, 600 mg, and 800 mg	Croscarmellose sodium, magnesium stearate and povidone.

INDICATIONS AND CLINICAL USE

Adults (≥18 years of age)
APTIOM (eslicarbazepine acetate) is indicated as:

- Monotherapy in the management of partial-onset seizures in adult patients with epilepsy. All patients who participated in the monotherapy trial were newly or recently diagnosed with epilepsy (see **CLINICAL TRIALS**).

- Adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

Geriatrics (>65 years of age)
There were insufficient numbers of elderly patients who completed partial-onset seizure controlled trials (N=39) to determine the safety and efficacy of APTIOM in this patient population. Caution should be exercised during dose titration, and age-associated decrease in renal clearance should be considered in elderly patients [see also **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; ADVERSE REACTIONS, Comparison of Gender, Age and Race,** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**].

Pediatrics (<18 years of age)
The safety and efficacy of APTIOM in pediatric patients have not been established. APTIOM is not indicated for use in this population [see also **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**].

CONTRAINDICATIONS

- Patients with a known hypersensitivity to APTIOM (eslicarbazepine acetate) or other carboxamide derivatives (e.g., carbamazepine, oxcarbazepine) or any of its components. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Patients with a history of, or presence of, second- or third-degree atrioventricular (AV) block.

WARNINGS AND PRECAUTIONS

General

Withdrawal of Antiepileptic Drugs (AEDs)
As with all AEDs, APTIOM (eslicarbazapine acetate) should be withdrawn gradually to minimize the potential of increased seizure frequency [see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**].

Cardiac Rhythm and Conduction Abnormalities

PR Interval Prolongation
APTIOM causes PR interval prolongation [see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**]. Caution should be observed in patients with first degree atrioventricular block, conduction disorders, a history of syncope or arrhythmia, angina, or ischemic heart disease. Such patients should receive careful monitoring, with ECG recordings at baseline and after titration of APTIOM to steady-state. Concomitant medications that result in a PR interval prolongation (e.g., carbamazepine, pregabalin, lamotrigine, beta-blockers) should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk [see **DRUG INTERACTIONS**].

In Phase III adjunctive epilepsy studies with APTIOM, the mean increase in PR interval at the end of 12 weeks maintenance treatment was 2.4 msec, 1.3 msec, and 2.6 msec in the 400, 800, and 1200 mg/day groups, respectively, and 0.6 msec in the placebo group. The mean maximum increase in PR interval in these controlled trials was 2.4 msec, 1.3 msec and 2.6 msec in the 400, 800, and 1200 mg/day groups, respectively, and 0.6 msec in the placebo group. A total of 9/1021 (0.8%) APTIOM patients and 1/426 (0.2%) placebo patients had a PR-interval value >200 msec at study end that was not present at baseline.

Patients with significant electrocardiographic (ECG) abnormalities were systematically excluded from these trials.

In a clinical pharmacology ECG trial of healthy subjects, the maximum mean difference from placebo in PR interval was 4.4 msec at 5 h post-dosing on day 5 in the 1200 mg (maximum recommended daily dose) treatment arm. For the 2400 mg (2 times maximum recommended daily dose) treatment arm, the maximum mean difference from placebo was 8.2 msec at 3 h post-dosing on day 5 [see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**].

Post-marketing cases of atrioventricular block have also been reported.

Heart Rate
In Phase III adjunctive epilepsy studies, the mean change in heart rate at the end of 12 weeks maintenance treatment was -0.5 bpm, 0.8 bpm, and -0.3 bpm in the 400, 800, and 1200 mg/day groups, respectively, and -0.6 bpm in the placebo group. In a clinical pharmacology ECG trial of healthy subjects, APTIOM was associated with a dose-dependent increase in heart rate [see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**]. The maximum mean difference

from placebo was 3.6 bpm and 6.8 bpm in the 1200 and 2400 mg dose groups, respectively. Caution should be observed in patients with cardiac conditions that could be worsened by an increase in heart rate, such as tachyarrhythmias or ischemic heart disease.

Atrial Fibrillation and Atrial Flutter
APTIOM administration may predispose patients to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with cardiovascular disease. Patients should be made aware of the symptoms of atrial fibrillation and flutter (e.g., palpitations, rapid or irregular pulse, shortness of breath) and told to contact their physician should any of these symptoms occur. One case of atrial flutter was reported in open-label epilepsy trials.

Hepatic/Biliary/Pancreatic

Drug-induced Liver Injury
Some APTIOM-treated patients experienced dose-independent elevations in transaminases >3 times upper limit of normal. In other cases [3/4940 (0.06%)] these elevations were accompanied by concomitant elevation (>2 times upper limit of normal) in total bilirubin. In the Phase III monotherapy epilepsy study, elevations in transaminases occurred in 0.7% (3/401) APTIOM-treated patients. The combination of transaminase elevations and elevated total bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury. APTIOM should be discontinued in patients with jaundice or laboratory evidence of liver injury suggestive of hepatic dysfunction (eg, nausea/vomiting, anorexia, pruritus, right upper quadrant pain, etc).

Hypersensitivity

Serious Dermatologic Reactions
Serious dermatologic reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with APTIOM use. Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have also been reported in patients using oxcarbazepine or carbamazepine which are chemically related to APTIOM. The reporting rate of these reactions associated with oxcarbazepine use exceeds the background incidence rate estimates by a factor of 3- to 10-fold. The reporting rates for APTIOM have not been determined. Risk factors for the development of serious dermatologic reactions with APTIOM use have not been identified.

If a patient develops a dermatologic reaction while taking APTIOM, discontinue APTIOM use, unless the reaction is clearly not drug-related. Patients with a prior dermatologic reaction with carboxamide derivatives such as oxcarbazepine, carbamazepine, or APTIOM should ordinarily not be treated with APTIOM.

Ancestry and Allelic Variation in the HLA-A Gene
There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS/TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese population.

The frequency of the HLA-A*3101 allele, an inherited allelic variant of the HLA-A gene, varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations with some exceptions within 5-12%.

Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10%-15% in other native ethnicities in these same regions.

There are insufficient data on patients treated with APTIOM to support a recommendation for testing the presence of HLA-A*3101 allele in patients prior to initiating treatment with APTIOM. Screening is generally not recommended for any current APTIOM users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Ancestry and Allelic Variation in the HLA-B Gene

In studies that included small samples of carbamazepine-treated patients of Han Chinese and Thai origin, a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Results of these studies suggest that the presence of the HLA-B*1502 allele may be one of the risk factors for anticonvulsant-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in these patients. Until further information is available, the use of APTIOM and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele unless the benefits clearly outweigh the risks. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low or in current APTIOM users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking APTIOM and other antiepileptic drugs. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately.

If a patient develops a skin reaction or DRESS while taking APTIOM, unless the reaction is clearly not drug-related, APTIOM should be discontinued and replaced by an alternative antiepileptic medication. APTIOM should not be used in patients with known hypersensitivity to or prior dermatologic reaction to carboxamide derivatives (e.g., carbamazepine, oxcarbazepine) [see **CONTRAINDICATIONS**].

Anaphylactic Reactions and Angioedema

Rare cases of anaphylaxis and angioedema have been reported in patients taking APTIOM. Anaphylaxis and angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with APTIOM, the drug should be discontinued. Patients with a prior anaphylactic-type reaction with APTIOM or other carboxamide derivatives (e.g., carbamazepine, oxcarbazepine) should not be treated with APTIOM [see **CONTRAINDICATIONS**].

Hyponatremia

Clinically significant hyponatremia (sodium <125 mEq/L) has been reported during APTIOM use in clinical trials and post-marketing use. Measurement of serum sodium and chloride levels should be considered during maintenance treatment with APTIOM, particularly if the patient is receiving other medications known to decrease serum sodium levels, and should be performed if symptoms of hyponatremia develop (e.g., nausea/vomiting, malaise, headache, lethargy, confusion, irritability, muscle weakness/spasms, obtundation, or increase in seizure frequency or severity). In three controlled adjunctive epilepsy studies, 1/196 patients (0.5%) treated with 400 mg, 4/415 patients (1.0%) treated with 800 mg, and 6/410 patients (1.5%) treated with 1200 mg of APTIOM had one or more serum sodium values less than 125 mEq/L during treatment (placebo: none). A higher percentage of the APTIOM-treated patients (5.1%) than placebo-treated patients (0.7%) experienced decreases in sodium values greater than 10 mEq/L. These effects were mostly dose-related, generally appeared within the first 8 weeks of treatment (as early as after 3 days) and, in some cases, led to APTIOM discontinuation. Serious, life-threatening complications were reported with APTIOM-associated hyponatremia (as low as 112 mEq/L) including seizures, severe nausea/vomiting leading to dehydration, severe gait instability, and injury. Some patients required hospitalization and permanent discontinuation of APTIOM. Concurrent hypochloremia was also present in some patients with hyponatremia. Many patients who developed hyponatremia were asymptomatic.

In the controlled monotherapy epilepsy trial, sodium decreases of >10 mEq/L were seen in 11.1% of APTIOM-treated patients. Sodium levels ≤125 mEq/L were found in 1.5% of APTIOM-treated patients.

Cases of symptomatic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported during post-marketing use. In clinical trials, patients whose treatment with APTIOM was discontinued because of hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment [see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**].

Measurement of serum sodium levels should be considered for patients during maintenance treatment with APTIOM, particularly if the patient has had a previous history of hyponatremia, has a condition [e.g., SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion)] or is receiving other medications known to decrease serum sodium level (e.g., diuretics, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity). If any degree of hyponatremia develops, APTIOM dose reduction or discontinuation and alternative anti-epileptic medication should be considered.

Abnormal Thyroid Function Tests

In controlled adjunctive epilepsy trials, the incidence of hypothyroidism in APTIOM 400 mg, 800 mg, and 1200 mg treatment groups was 0%, 1.0%, and 1.2%, respectively (placebo: 0.7%). Hypothyroidism led to discontinuation of one patient (0.2%) in the APTIOM 1200 mg treatment group. In the controlled monotherapy epilepsy trial, the incidence of hypothyroidism in APTIOM-treated patients was 2.5% (10/401). Dose-dependent decreases in serum T_3 and T_4 (free and total) values have also been observed in patients taking APTIOM. Abnormal thyroid function tests should be clinically evaluated.

Neurologic

Dizziness and Disturbance in Gait and Coordination
APTIOM causes dose-related increases in adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, ataxia, vertigo, balance disorder, gait disturbance, nystagmus, and abnormal coordination), which could increase the occurrence of accidental injury or falls. In controlled adjunctive therapy epilepsy trials, these events were reported in 22% (43/196), 26% (107/415), and 38% (155/410) of patients randomized to receive APTIOM at doses of 400 mg, 800 mg, and 1200 mg/day, respectively, compared to 12% (52/426) of placebo-treated patients. Events related to dizziness and disturbance in gait and coordination were more often serious in APTIOM-treated patients than in placebo-treated patients (2% vs. 0%), and more often led to study withdrawal in APTIOM-treated patients than in placebo-treated patients (9% vs. 0.7%). There was an increased risk of these adverse reactions during the titration period (compared to the maintenance period) and there also may be an increased risk of these adverse reactions in patients 60 years of age and older compared to younger adults. Nausea and vomiting also occurred with these events.

The incidence of dizziness was greater with the concomitant use of APTIOM and carbamazepine compared to the use of APTIOM without carbamazepine (up to 37% vs. 19%, respectively, in controlled adjunctive epilepsy trials). Therefore, consider dosage modifications of both APTIOM and carbamazepine if these drugs are used concomitantly [see **DRUG INTERACTIONS, Drug-Drug Interactions**].

In the controlled monotherapy epilepsy trial, the incidences of dizziness and headache in the APTIOM-treated patients were 13.7% (55/401) and 22.9% (92/401), respectively.

Somnolence and Fatigue
APTIOM causes dose-dependent increases in somnolence and fatigue-related adverse reactions (fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy). In the controlled adjunctive epilepsy trials, these events were reported in 13% (57/426) of placebo patients, 18% (36/196) of patients randomized to receive 400 mg, 16% (67/415) of patients randomized to receive 800 mg/day APTIOM, and 28% (115/410) of patients randomized to receive 1200 mg/day APTIOM. Somnolence and fatigue-related events were serious in 0.3% of APTIOM-treated patients (and 0 placebo patients) and led to discontinuation in 3% of APTIOM-treated patients (and 0.7% of placebo-treated patients).

In the controlled monotherapy epilepsy trial, the incidence of somnolence in APTIOM-treated patients was 6.7% (27/401).

Cognitive Dysfunction
APTIOM causes dose-dependent increases in cognitive dysfunction-related events (memory impairment, disturbance in attention, amnesia, confusional state, aphasia, speech disorder, slowness of thought, disorientation, and psychomotor retardation). In the controlled adjunctive epilepsy trials, these events were reported in 1% (6/426) of placebo patients, 4% (7/196) of patients randomized to receive 400 mg APTIOM, 4% (16/415) of patients randomized to receive 800 mg/day APTIOM, and 7% (27/410) of patients randomized to receive 1200 mg/day APTIOM. Cognitive dysfunction-related events were serious in 0.2% of APTIOM-treated patients (and 0.2% of placebo patients) and led to discontinuation in 1% of APTIOM-treated patients (and 0.5% of placebo-treated patients).

In the controlled monotherapy epilepsy trial, the incidences of memory impairment, disturbance in

attention, confusional state, aphasia, slow speech, and disorientation in APTIOM-treated patients were 2.2% (9/401), 2.5% (10/401), 0.7% (3/401), 0.3% (1/401), 0.3% (1/401), and 0.5% (2/401), respectively.

Ophthalmological Effects

APTIOM causes dose-dependent increases in events related to visual changes including diplopia, blurred vision, and impaired vision. In the controlled adjunctive therapy epilepsy trials, these events were reported in 6% (25/426) of placebo patients, 12% (24/196) of patients randomized to receive 400 mg APTIOM, 16% (67/415) of patients randomized to receive 800 mg/day APTIOM, and 17% (69/410) of patients randomized to receive 1200 mg/day APTIOM. Eye events were serious in 0.7% of APTIOM-treated patients (and 0 placebo patients) and led to discontinuation in 4% of APTIOM-treated patients (and 0.2% of placebo-treated patients). There was an increased risk of these adverse reactions during the titration period (compared to the maintenance period) and also in patients 60 years of age and older (compared to younger adults). The incidence of diplopia was greater with the concomitant use of APTIOM and carbamazepine compared to the use of APTIOM without carbamazepine (up to 16% vs. 6%, respectively).

In the controlled monotherapy epilepsy trial, the incidences of diplopia, blurred vision, and impaired vision in APTIOM-treated patients were 0.5% (2/401), 2.0% (8/401), and 0.7% (3/401).

Patients should be informed that, if visual disturbances occur, they should notify their physician promptly. If visual disturbance persists, further assessment, including dose reduction and possible discontinuation of APTIOM, should be considered. More frequent assessments should be considered for patients with known vision-related issues or those who are already routinely monitored for ocular conditions.

Bone Disorders

Long-term use of antiepileptics such as carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine, and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones.

Hematologic

Rare cases of pancytopenia and agranulocytosis have been reported during post-marketing use in patients treated with APTIOM. Cases of leukopenia have been reported in clinical trials and during post-marketing use.

Discontinuation of APTIOM and replacement with alternative antiepileptic medication should be considered if there is evidence of clinically relevant bone marrow depression.

Caution with Driving and Use of Machinery

APTIOM can cause dizziness and somnolence and therefore may influence the ability of the patient to drive or use dangerous machinery. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities requiring mental alertness, until they know how APTIOM affects them [see also **WARNINGS AND PRECAUTIONS, Neurologic, Dizziness and Disturbance in Gait and Coordination**].

Psychiatric

Suicidal Ideation and Behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drugs). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Abuse
In a human abuse study in recreational sedative abusers, APTIOM showed no evidence of abuse. In Phase I studies, 1.5% of the healthy volunteers taking APTIOM reported euphoria compared to 0.4% taking placebo.

Dependence/Liability
The potential for APTIOM to produce withdrawal symptoms has not been adequately evaluated. In general, antiepileptic drugs should not be abruptly discontinued in patients with epilepsy because of the risk of increased seizure frequency and status epilepticus.

Renal

APTIOM metabolites are eliminated from the systemic circulation primarily by renal excretion. A study in patients with mild to severe renal impairment showed that clearance is dependent on renal function. During treatment with APTIOM, dose adjustment is recommended in patients with creatinine clearance <50 mL/min. Hemodialysis removes APTIOM metabolites from plasma [see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**].

Special Populations

Women of Childbearing Potential and Hormonal Contraceptives

Use of APTIOM with oral contraceptives containing ethinylestradiol and levonorgestrel at doses of 800 mg and 1200 mg has been shown to decrease mean ethinylestradiol exposure by 31% and 42%, respectively, and to decrease mean levonorgestrel exposure by 17% and 37%, respectively. Therefore, use of APTIOM at any dose with hormonal contraceptives may render them less effective and additional or alternative non-hormonal birth control methods should be used [see **DRUG INTERACTIONS**].

Pregnant Women

There are no studies with APTIOM in pregnant women.

In some animal species, administration of APTIOM resulted in developmental toxicity and induction of fetal malformations and growth retardation [see **TOXICOLOGY, Reproduction and Development Toxicology**].

Since the potential risk for humans is unknown, APTIOM should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. If a woman plans to become pregnant while taking APTIOM, the use of this product should be carefully re-evaluated.

Pregnancy Registry

Physicians are advised to recommend that pregnant patients taking APTIOM enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling 1-888-233-2334 (toll-free), and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Labour and Delivery

The effects of APTIOM on labour and delivery in pregnant women are unknown.

Nursing Women

Eslicarbazepine is excreted in human breast milk. Because of the potential for serious adverse reactions to APTIOM in nursed infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

Fertility

The effects of APTIOM on fertility in humans are unknown [see **TOXICOLOGY, Reproduction and Development Toxicology**].

Pediatrics (<18 years of age)

The safety and efficacy of APTIOM in pediatric patients have not been established [see also **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**].

Geriatrics (>65 years of age)

There were insufficient numbers of elderly patients who received APTIOM doses up to 1200 mg/day and completed the controlled adjunctive and monotherapy trials in patients with partial-onset seizures (N = 38) to determine the safety and efficacy of APTIOM in this patient population. In the controlled monotherapy trial-in patients with partial-onset seizures, only 1 elderly patient received APTIOM 1600

mg/day and completed the trial. Thus, APTIOM doses higher than 1200 mg/day are not recommended in the elderly population (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In adjunctive therapy controlled and uncontrolled trials in patients with partial-onset seizures, 1192 patients have received APTIOM (eslicarbazepine acetate) of whom 586 have been treated for longer than 6 months and 462 for longer than 12 months. In the controlled monotherapy trial in patients with partial-onset seizures, 401 patients received APTIOM and 412 received carbamazepine-controlled release (CBZ-CR); 70.8% of patients in the APTIOM group and 74.8% of patients in the CBZ-CR group completed the 26-week Evaluation Period.

Monotherapy
Adverse reactions observed in the monotherapy trial were generally similar to those observed and attributed to APTIOM in adjunctive placebo-controlled trials (see below). Treatment-emergent adverse events reported in >2% of the APTIOM-treated patients included hyponatremia [3.0% (12/401)], dizziness [13.7% (55/401)], somnolence [6.7% (27/401)], and headache [22.9% (92/401)].

Adjunctive Therapy
Some of the most frequently reported adverse reactions in controlled adjunctive epilepsy trials with APTIOM were dizziness, somnolence, headache, nausea, diplopia, vomiting, fatigue, ataxia, vision blurred, and vertigo. Most adverse events typically demonstrated a dose-response.

The majority of adverse events in the APTIOM-treated patients were of mild to moderate intensity. The most frequently reported adverse events in controlled adjunctive epilepsy trials predominantly occurred during the first few weeks of treatment with APTIOM. Adverse events during titration were less frequent for patients who began therapy at an initial daily dose of 400 mg for 1 week and then escalated to 800 mg/day as compared to patients who initiated therapy at the daily dose of 800 mg.

The adverse event profile observed during the long-term adjunctive open label extension studies in more than 460 patients who completed the open-label phase was similar to that observed during the placebo controlled, Phase III clinical trials.

Discontinuations Due to Adverse Events in Controlled Clinical Studies
Monotherapy
Overall, 13.5% of APTIOM patients and 18.0% of CBZ-CR patients discontinued treatment due to TEAEs. The adverse events most frequently leading to discontinuation in the APTIOM group were fatigue (1.7%) and disturbance in attention (0.7%).

Adjunctive Therapy
In the Phase III, controlled, adjunctive treatment epilepsy trials, the rate of discontinuation as a result of any adverse event was 8.7% for the 400 mg arm, 13.5% for the 800 mg arm and 24.4% for the 1200 mg treatment group (placebo: 6.1%). The adverse events most frequently (>2% in any APTIOM treatment group and greater than placebo) leading to discontinuation were dizziness, ataxia, somnolence, nausea, vomiting, diplopia, vision blurred, and vertigo.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1. Treatment Emergent Adverse Events Incidence in Controlled, Adjunctive Phase III, Clinical Trials of Adjunctive Epilepsy Therapy in Adults (Studies 301, 302, and 304; Events ≥2% of Patients in the APTIOM 400 mg, 800 mg, or 1200 mg Dose Group and More Frequent Than in the Placebo Group)

System Organ Class/ Preferred Term	Placebo	APTIOM		
		400 mg	800 mg	1200 mg
	(N=426) %	(N = 196) %	(N=415) %	(N=410) %
Ear and labyrinth disorders				
Vertigo	<1	4	2	6
Eye disorders				
Diplopia[1]	**2**	**7**	**9**	**11**
Vision blurred	1	5	6	5
Visual impairment	1	0	2	1
Gastrointestinal disorders				
Nausea[1]	**5**	**9**	**10**	**16**
Vomiting[1]	**3**	**5**	**6**	**10**
Diarrhea	3	2	4	2
Constipation	1	4	2	2
Abdominal pain	1	2	2	2
Gastritis	<1	0	2	<1
General disorders and administration site conditions				
Fatigue	4	3	4	7
Asthenia	2	2	2	3
Gait disturbance	<1	2	2	2
Edema peripheral	1	0	2	1
Injury, poisoning and procedural complications				
Fall	1	2	3	1
Metabolism and nutrition disorders				
Hyponatraemia	<1	<1	2	2
Nervous system disorders				
Dizziness[1]	**9**	**16**	**20**	**28**
Somnolence	8	14	11	18
Headache[1]	**9**	**12**	**13**	**15**
Ataxia	2	4	4	6
Balance disorder	<1	<1	3	3
Tremor[1]	**<1**	**<1**	**2**	**4**
Dysarthria	0	0	1	2
Memory impairment	<1	1	1	2
Nystagmus	<1	1	1	2
Psychiatric disorders				
Depression	2	3	1	3
Insomnia	1	2	2	2
Skin and subcutaneous tissue disorders				
Rash[1]	**1**	**<1**	**1**	**3**

[1]Events highlighted in bold are dose dependent.

Some adverse reactions (e.g., diplopia, ataxia, dizziness, somnolence, nausea, vomiting) may occur more frequently when patients take APTIOM and carbamazepine concomitantly. When APTIOM and carbamazepine are taken concomitantly, the dose of APTIOM or carbamazepine may need to be adjusted based on efficacy and tolerability [see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**].

In the Phase III adjunctive and monotherapy studies for APTIOM, no clinically relevant ECG abnormalities or changes in ECG parameters were observed when compared to placebo.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Other adverse reactions reported in the controlled Phase III adjunctive trials in < 2% of patients treated with APTIOM and numerically greater than placebo were aphasia, coordination abnormal, disorientation, disturbance in attention, dry mouth, dyspnea, hypothyroidism, leukopenia, myalgia, nervousness, paraesthesia, and pruritus.

Comparison of Gender, Age and Race

In the controlled adjunctive epilepsy trials, the overall adverse event rate was similar in male and female patients. Adverse event rates in over 400 patients aged ≥60 and <60 were comparable. Although there were few non-Caucasian patients (19%) in controlled epilepsy trials, no differences in the frequency of adverse events in non-Caucasian patients compared to Caucasian patients were observed.

In the controlled monotherapy epilepsy trial, the overall adverse event rates were comparable between treatment groups by gender and race. There was a higher incidence of overall adverse events in patients ≥65 years of age versus those <65 years of age, however, the rates in both age groups were comparable between treatment groups.

Post-Market Adverse Drug Reactions

Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

The following adverse reactions have been reported with APTIOM in post-marketing experience: hyponatraemia, dizziness, medication error, blood sodium decreased, partial seizures, overdose, fatigue, vertigo, rash, diplopia, pruritus, nausea, headache, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), toxic epidermal necrolysis (TEN), agranulocytosis, thrombocytopenia, megaloblastic anemia, pancytopenia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), angioedema, and urticaria.

Hyponatremia
Hyponatremia is among the most frequently reported adverse drug reactions in the post-marketing database for APTIOM. Of the cases reported (a total of 285 cases), 10.5% occurred at doses of APTIOM above the maximum recommended daily dose of 1600 mg and 89.5% occurred within the range of recommended daily dosing (400 to 1600 mg) for epilepsy. The dose was unknown for the remaining cases.

Most patients experienced sodium levels between 120 and 130 mEq/L but a sodium level of 103 mEq/L was reported in one patient. Two other patients had sodium values of 110 and 111 mEq/L. Complications of very low plasma sodium levels (<120 mEq/L) including convulsions and confusional state were reported in 6 patients. In some instances (11% of cases), hyponatremia resolved following APTIOM dose reduction or permanent discontinuation (see **WARNINGS AND PRECAUTIONS, Hyponatremia**).

DRUG INTERACTIONS

Overview

APTIOM can inhibit CYP2C19, which can cause increased plasma concentrations of drugs that are substrates of this isoenzyme. *In vivo* studies suggest that APTIOM can decrease exposure of CYP3A4 substrates. In addition, several AEDs that are enzyme inducers can decrease plasma concentrations of APTIOM.

Drug-Drug Interactions

The potential interactions between APTIOM and anti-epileptic drugs are summarized in Table 2.

Table 2. Potential Interactions Between APTIOM and Concomitant Antiepileptic Drugs

AED Coadministered	AED Dose (mg/day) evaluated	Population and Number of Subjects	APTIOM Dose (mg/day) evaluated	Influence of APTIOM on AED	Influence of AED on APTIOM	Dosage Adjustment
Carbamazepine[a, b]	200-4200	N = 1039 patients[a] N = 38 healthy volunteers[b]	1200	4-10% decrease in exposure	25-47% decrease in exposure	May need lower dose of carbamazepine based on tolerability May need higher dose of APTIOM based on need for additional seizure control
Phenobarbital[a, c]	25-600	N = 1039 patients[a]	1200	No influence	34% decrease in exposure	May need higher dose of APTIOM
Phenytoin[a]	100-700[a] 300[b]	N = 1039 patients[a] N = 32 healthy volunteers[b]	1200 1200	35% increase in exposure	33% decrease in exposure	Monitor plasma phenytoin concentration; in epilepsy, dose adjustment may not be necessary and may need higher dose of APTIOM
Valproate[a]	200-5500	N = 1039 patients[a]	1200	No influence	No influence	None
Lamotrigine[b]	150	N = 32 healthy volunteers[b]	1200	14% decrease in exposure	4% decrease in exposure	None
Topiramate[b]	200	N = 32 healthy volunteers[b]	1200	18% decrease in exposure	7% decrease in exposure	None
Levetiracetam[a]	250-6000	N = 1039 patients[a]	1200	No influence	No influence	None
Gabapentin[a]	300-3600	N = 1039 patients[a]	1200	No influence	No influence	None

[a] Indicates the results in epilepsy patients (population PK analysis including 11 Phase I and 3 Phase III trials; N = 1039).
[b] Indicates the results in healthy volunteers.
[c] Includes other AED enzyme inducers.

The potential effects of APTIOM on the exposure of concomitant drugs are summarized in Table 3.

Table 3. Potential Interactions Between APTIOM and Other Concomitant Drugs

Concomitant Drug	Concomitant Dose Evaluated	Population and Number of Subjects	APTIOM Dose (mg) Evaluated	Effect on Exposure (AUC) of Concomitant Drug	Dosage Adjustment
Warfarin	5 mg	N = 13 healthy volunteers	1200	S-Warfarin: 23% decrease R-Warfarin: 2% decrease No change in prothrombin time ratios	Patients should be monitored to maintain INR.
Simvastatin	80 mg	N = 24 healthy volunteers	800	50% decrease	Adjust dose of simvastatin if a clinically significant change in lipids is noted.
Rosuvastatin	40 mg	N = 33 healthy volunteers	1200	39% decrease	Adjust dose of rosuvastatin if a clinically significant change in lipids is noted.
Oral Contraceptive: (ethinylestradiol and levonorgestrel)	30 μg ethinylestradiol + 150 μg levonorgestrel	N = 20 healthy volunteers	1200 800	Ethinylestradiol: 42% decrease Levonorgestrel: 37% decrease Ethinylestradiol: 31% decrease Levonorgestrel: 17% decrease	Additional or alternative non-hormonal birth control should be used when APTIOM at any dose is used concomitantly with oral contraceptives.
Metformin	850 mg	N = 20 healthy volunteers	1200	5% decrease	None
Digoxin	0.5 mg / 0.25 mg	N = 12 healthy volunteers	1200	4% decrease in exposure 15% decrease in C_{max}	None

Drugs that Prolong the PR Interval

APTIOM causes PR interval prolongation [see **WARNINGS AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities** and **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**]. The concomitant use of APTIOM with other drugs that prolong the PR interval, including, but not limited to, beta-blockers, antiarrhythmics, non-dihydropyridine calcium channel blockers, digitalis glycosides, α_2-adrenoreceptor agonists, cholinesterase inhibitors, lacosamide, carbamazepine, pregabalin, lamotrigine, sphingosine-1 phosphate receptor modulators (e.g., fingolimod), and some HIV protease inhibitors, should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interferences with laboratory tests have not been studied

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Monotherapy
The recommended starting dose of APTIOM (eslicarbazepine acetate) is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. Based on individual response and tolerability, the dose may be increased to 1200 mg once daily. In the monotherapy trial, the majority of patients who completed the Evaluation Period of the study and remained seizure free, received APTIOM 800 or 1200 mg/day (see **CLINICAL TRIALS**). Some patients who do not achieve a satisfactory response at APTIOM 1200 mg/day, may benefit from a dose of 1600 mg once daily.

Adjunctive Therapy
The recommended starting dose of APTIOM is 400 mg once daily which should be increased to the recommended maintenance dose of 800 mg once daily after one or two weeks. For some patients, therapy may be initiated at 800 mg once daily if the need for seizure control outweighs a potentially increased risk of adverse events during initiation. Based on individual response and tolerability, the dose may be increased to a maximum of 1200 mg once daily. A maximum dose of 1200 mg once daily (administered as one and a half 800 mg tablets) should only be initiated after the patient has been treated with 800 mg once daily for at least one week. In controlled clinical trials, the higher dose (1200 mg once daily) was not always significantly more efficacious than the 800 mg once daily dose and patients treated with this higher dose experienced more severe and frequent adverse reactions and discontinued the trial more frequently.

Patients with Renal Impairment
In patients with moderate or severe renal impairment (i.e., creatinine clearance < 50 mL/min), the initial, titration, and maintenance doses should generally be reduced by 50%. Titration and maintenance doses may be adjusted according to clinical response and tolerability [see **ACTION AND CLINICAL PHARMACOLOGY**].

Hemodialysis
In subjects without epilepsy with end stage renal disease (N = 8), repeated hemodialysis removed APTIOM metabolites from systemic circulation. There is no data on the effects of hemodialysis in patients with epilepsy. Thus, patients with end-stage renal disease who undergo dialysis should be treated with caution as dose adjustments may be necessary.

Patients with Hepatic Impairment
Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of APTIOM in patients with severe hepatic impairment has not been studied and is not recommended [see **ACTION AND CLINICAL PHARMACOLOGY**].

Geriatrics (>65 years of age)
There were insufficient numbers of elderly patients who completed controlled adjunctive partial-onset seizure trials (N=12) [see also **INDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**]. Due to a very small number of elderly patients (n= 1) who received

APTIOM 1600 mg/day and completed the controlled monotherapy study, this dose is not recommended for the elderly population.

Pediatrics (<18 years of age)
The safety and efficacy of APTIOM in pediatric patients have not been established. APTIOM is not indicated for use in this population [see also **INDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**].

Missed Dose

If a dose is missed, it should be taken as soon as possible. Dosing should then continue as scheduled.

Administration

APTIOM can be administered as whole or crushed tablets, taken with or without food.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is limited clinical experience with APTIOM (eslicarbazepine acetate) overdose in humans. The highest reported dose in cases of post-marketing overdose was 32 g taken as a suicide attempt; the patient recovered.

There is no specific antidote for overdose with APTIOM. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

Standard hemodialysis procedures result in significant clearance of APTIOM. Hemodialysis has not been performed in a case of overdose, but may be indicated based on the patient's clinical state or in patients with significant renal impairment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which APTIOM (eslicarbazepine acetate) exerts its antiepileptic effect in humans is unknown [see **DETAILED PHARMACOLOGY, Preclinical Safety Pharmacology** for experimental *in vitro* and *in vivo* data in animals].

Pharmacodynamics

After oral administration, APTIOM is extensively converted to its major active metabolite, eslicarbazepine. In humans, the pharmacological activity of APTIOM is primarily exerted through eslicarbazepine.

Cardiac Electrophysiology

A randomized, double-blind, placebo-controlled, 4-period crossover trial was performed to evaluate the effect of APTIOM on ECG parameters in healthy subjects (N=67). APTIOM was administered for 5 days at doses of 1200 mg/day (maximum recommended daily therapeutic dose) and 2400 mg/day (2 times maximum recommended daily therapeutic dose). Serial ECG data were collected at baseline and on day 5 of treatment.

APTIOM was associated with a dose- and concentration-dependent increase in heart rate. At the 1200 mg dose, the maximum mean difference from placebo was 3.6 bpm (90% CI 1.5, 5.7) at 6 h post-dosing on day 5. At the 2400 mg dose, the maximum mean difference from placebo was 6.8 bpm (90% CI 4.5, 9.1) at 8 h post-dosing on day 5 [see **WARNINGS AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities**].

APTIOM caused a dose- and concentration-dependent prolongation of the PR interval. For the 1200 mg treatment, the maximum mean difference from placebo was 4.4 ms (90% CI 2.1, 6.8) at 5 h post-dosing on day 5. For the 2400 mg treatment, the maximum mean difference from placebo was 8.2 ms (90% CI 5.3, 11.1) at 3 h post-dosing on day 5 [see **WARNING AND PRECAUTIONS, Cardiac Rhythm and Conduction Abnormalities; DRUG INTERACTIONS, Drugs that Prolong the PR Interval**].

APTIOM was associated with shortening of the QTcF interval ($QTcF=QT/RR^{0.33}$). For the 1200 mg dose, the maximum mean difference from placebo was -6.4 ms (90% CI -9.4, -3.4) at 4 h post-dosing on day 5, whilst for the 2400 mg dose, the maximum mean difference from placebo was -5.2 ms (90% CI -8.9, -1.6) at 3 h post-dosing on day 5.

Pharmacokinetics

The pharmacokinetics of eslicarbazepine is linear and dose-proportional in the dose range of 200 mg to 1200 mg once daily, both in healthy subjects and patients. The apparent half-life of eslicarbazepine in plasma was 10-20 hours in healthy subjects and 13-20 hours in patients with epilepsy. Steady-state plasma concentrations are attained after 4 to 5 days of once daily dosing. At steady state, there is less fluctuation of concentration from peak to trough in cerebrospinal fluid than in plasma and the apparent half-life of eslicarbazepine in the cerebrospinal fluid is approximately 24 hours.

Table 4. Mean (SD) Pharmacokinetic Parameters of Eslicarbazepine in Patients with Epilepsy Following Once Daily Dosing of Eslicarbazepine Acetate [Study 301 PK Substudy]

Eslicarbazepine Acetate Dose	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-24} ng*h/mL	t_{max}[1] (h)
400 mg (N=7)	9673 (5142)	12.8 (5.07)	132514 (89477)	2.00 (1.00-6.00)
800 mg (N=26)	15462 (5000)	13.5* (6.06)	205359 (74584)	2.00 (1.00-6.00)
1200 mg (N=18)	22957 (5263)	20.2 (10.9)	336147 (81654)	2.50 (1.00-6.50)

[1] t_{max} values are medians with ranges in parentheses; *N=25

Absorption: APTIOM is mostly undetectable (0.01% of the systemic exposure) after oral administration. Eslicarbazepine, the major metabolite, is primarily responsible for the pharmacological effect of APTIOM. Peak plasma concentrations (C_{max}) of eslicarbazepine are attained at 1-4 hours post-dose. Eslicarbazepine is highly bioavailable because the amount of eslicarbazepine and glucuronide metabolites recovered in urine corresponded to more than 90% of an APTIOM dose. Food has no effect on the pharmacokinetics of eslicarbazepine after oral administration of APTIOM.

Distribution: The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent of concentration. *In vitro* studies have shown that plasma protein binding was not relevantly affected by the presence of warfarin, diazepam, digoxin, phenytoin or tolbutamide. Similarly, the binding of warfarin, diazepam, digoxin, phenytoin or tolbutamide was not significantly affected by the presence of eslicarbazepine. The apparent volume of distribution of eslicarbazepine is 61.3 L.

Metabolism: APTIOM is rapidly and extensively metabolized to its major active metabolite, eslicarbazepine, by hydrolytic first-pass metabolism. Eslicarbazepine corresponds to about 92% of systemic exposure. The systemic exposure to minor active metabolites, including (R)-licarbazepine and oxcarbazepine, is <5%. The inactive glucuronides of these active metabolites correspond to about 3% of systemic exposure.

In *in vitro* studies in human liver microsomes, eslicarbazepine had no clinically relevant inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4, and only a moderate inhibitory effect on CYP2C19. Studies with eslicarbazepine in fresh human hepatocytes showed no induction of enzymes involved in glucuronidation and sulfation of 7-hydroxy-coumarin. A mild activation of UGT1A1 mediated glucuronidation was observed.

No apparent autoinduction of metabolism has been observed with APTIOM in humans.

Excretion: APTIOM metabolites are eliminated from the systemic circulation primarily by renal excretion, in the unchanged and glucuronide conjugate forms. In total, eslicarbazepine and its glucuronide account for more than 90% of the total metabolites excreted in urine, approximately two thirds in the unchanged form and one third as glucuronide conjugate. Other minor metabolites account for the remaining 10% excreted in the urine. In healthy subjects with normal renal function, the renal clearance of eslicarbazepine (approximately 20 mL/min) is substantially lower than glomerular

filtration rate (80-120 mL/min), suggesting that renal tubular reabsorption occurs. The apparent plasma half-life of eslicarbazepine was 10-20 hours in healthy subjects and 13-20 hours in epilepsy patients.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of APTIOM in pediatric populations (<18 years of age) have not been established.

Geriatrics: The pharmacokinetic profile of eslicarbazepine was unaffected in elderly subjects with creatinine clearance >60 mL/min compared to healthy, younger subjects (18-40 years) after single and repeated doses of 600 mg APTIOM during 8 days of dosing. No dose adjustment is necessary in adults based on age, if CrCL is ≥50 mL/min.

Gender: Studies in healthy subjects and patients showed that pharmacokinetics of eslicarbazepine were not affected by gender.

Race: No clinically significant effect of race (Caucasian N=849, Black N=53, Asian N=65, and Other N=51) on the pharmacokinetics of eslicarbazepine was noted in a population pharmacokinetic analysis of pooled data from the Phase I studies and Phase III epilepsy clinical trials.

Hepatic Impairment: The pharmacokinetics and metabolism of APTIOM were evaluated in 8 healthy subjects and 8 patients without epilepsy with moderate liver impairment (Child-Pugh B; 7-9 points on the Child-Pugh assessment scale) after multiple oral doses. Moderate hepatic impairment did not affect the pharmacokinetics of APTIOM. No dose adjustment is recommended in patients with mild to moderate liver impairment.

The pharmacokinetics of APTIOM have not been studied in patients with severe hepatic impairment (Child-Pugh C; 10-15 points on the Child-Pugh assessment scale) and its use is not recommended in these patients [see **DOSAGE AND ADMINISTRATION**].

Renal Impairment: APTIOM metabolites are eliminated from the systemic circulation primarily by renal excretion. In a study of patients without epilepsy with varying degrees of renal impairment, following administration of a single 800 mg dose of APTIOM, the extent of systemic exposure of eslicarbazepine was increased by 62% in patients with mild renal impairment [Creatinine Clearance (CrCl) 50-80 mL/min (N=8)], by 2-fold in patients with moderate renal impairment [CrCl 30-50 mL/min (N=8)], and by 2.5-fold in patients with severe renal impairment [CrCl <30 mL/min (N=8)] in comparison to the healthy subjects [CrCl >80 mL/min (N=8)]. Dose adjustment is recommended in patients with creatinine clearance below 50 mL/min [see **DOSAGE AND ADMINISTRATION]**.

Hemodialysis
In patients with end stage renal disease (N = 8) without epilepsy, repeated hemodialysis removed APTIOM metabolites from systemic circulation. There is no data in patients with epilepsy. Thus, caution should be used when treating patients with end-stage renal [see **DOSAGE AND ADMINISTRATION**].

STORAGE AND STABILITY
Store at 15 – 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APTIOM (eslicarbazepine acetate) is supplied as white tablets for oral administration and is available in four tablet strengths containing 200 mg, 400 mg, 600 mg, and 800 mg of eslicarbazepine acetate. The 200 mg, 600 mg, and 800 mg tablets are white oblong and engraved with ESL 200, ESL 600, and ESL 800, respectively, on one side and scored on the other. The 400 mg tablets are circular biconvex and engraved with ESL 400 on one side.

APTIOM tablets also contain the following inactive ingredients: croscarmellose sodium, magnesium stearate and povidone.

200 mg: Bottles of 30; 400 mg: Bottles of 30; 600 mg: Bottles of 60 and 90; 800 mg: Bottles of 30 and 90.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

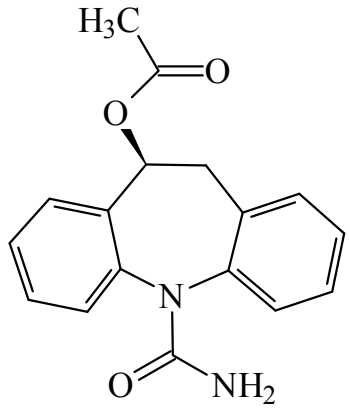
Proper name: Eslicarbazepine acetate

Chemical name: (S)-enantiomer, is (S)-10-Acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

Molecular formula and molecular mass: $C_{17}H_{16}N_2O_3$

M.W. = 296.32

Structural formula:



Physicochemical properties: Eslicarbazepine acetate is a white to off-white, odorless crystalline solid.

Eslicarbazepine acetate is insoluble in hexane, very slightly soluble in aqueous solvents and soluble in organic solvents such as acetone, acetonitrile, and methanol.

CLINICAL TRIALS

Monotherapy

STUDY 311

Study Demographics and Trial Design
The efficacy of APTIOM (eslicarbazepine acetate) as monotherapy in the treatment of partial-onset seizures has been demonstrated in a double-blind, active controlled, non-inferiority study, involving 401 patients who received APTIOM (800 to 1600 mg/day) and 412 patients who received carbamazepine controlled release (CBZ-CR; 400 to 1200 mg/day). Patients ranged in age between 18 and 85 years (mean: 38 years). All patients had newly or recently diagnosed epilepsy with at least 2 well documented, unprovoked, clinically evaluated and classified partial-onset seizures. Patients had to present with at least 1 seizure during the previous 3 months. Former or current use of any AED was prohibited, except for use of a single AED for a maximum duration of 2 weeks before Screening and with a drug-free period of at least 5 days before Randomization. A total of 27 elderly patients took at least one dose of APTIOM. Approximately 57% of the patients in the APTIOM treatment arm were male.

APTIOM was tested at once-daily doses of 800 mg, 1200 mg, and 1600 mg. The doses of the active comparator, CBZ-CR, were 200 mg, 400 mg, and 600 mg, twice-daily. After a screening period of up to 7 days, patients were randomly assigned to enter a 1-week Titration Period during which they received either APTIOM 400 mg once daily or CBZ-CR 200 mg once daily before increasing to the first target dose (APTIOM 800 mg once daily or CBZ-CR 200 mg twice daily). This was followed by a 1-week Stabilization Period and a 26-week Evaluation Period. All patients were randomized to the lowest dose level of each drug and only if a seizure occurred, patients were to be escalated to the next dose level. From the 815 randomized patients, 401 patients were treated with APTIOM once-daily [271 patients (67.6%) remained at dose of 800 mg, 70 patients (17.5%) remained at dose of 1200 mg, and 60 patients (15.0%) were treated with 1600 mg]. Among patients-randomized to APTIOM, 77.1% completed the Evaluation Period of the trial. Following the Evaluation Period, patients who had remained seizure-free at a specific dose (800, 1200, or 1600 mg/day), were entered into the Maintenance Period for an additional 26 weeks.

The primary efficacy end-point was the proportion of patients in the Per Protocol population who were seizure free for the entire 26-week of the Evaluation Period at the last received dose level.

Study Results
APTIOM met the pre-defined primary efficacy end-point and was considered to be non-inferior to CBZ-CR.

In the primary efficacy analysis, in which drop-outs were considered as non-responders, 71.1% of the patients were classified as seizure free in the APTIOM group and 75.6% in the CBZ-CR arm during 26 week Evaluation Period (see Table 5).

Table 5: Number and Percentage of the Patients Who Completed 26-Week Evaluation Phase and Remained Seizure Free at the Last Evaluated Dose (Per Protocol Set).

Parameter	26 weeks	
	APTIOM	**CBZ-CR**
Overall, n Seizure free for 26 weeks, n (%)	388 276 (71.1)	397 300 (75.6)
Last Evaluated Dose Level		
Dose level A, n Seizure free for 26 weeks, n (%)	246 210 (85.4)	285 237 (83.2)
Dose level B, n Seizure free for 26 weeks, n (%)	58 43 (74.1)	53 47 (88.7)
Dose level C, n Seizure free for 26 weeks, n (%)	53 23 (43.4)	32 16 (50)

CBZ-CR: Carbamazepine-Controlled Release; Per Protocol Set: Patients in the Full Analysis Set without major protocol violations

Note: Dose level A=APTIOM 800mg/day or CBZ-CR 200 mg BID; Dose level B=APTIOM 1200mg/day or CBZ-CR 400mg BID; Dose level C=APTIOM 1600mg/day or CBZ-CR 600 mg BID.

Other efficacy endpoints such as estimates of 12-month seizure freedom rates were supportive of the primary efficacy end-point.

The 6-month seizure freedom rates observed in patients aged 65 or older, by race, and by gender were similar between both treatment groups and the overall patient population.

Adjunctive Therapy

Study Demographics and Trial Design

The efficacy of APTIOM as adjunctive therapy in the treatment of partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, fixed-dose, multicenter trials in adult patients with epilepsy. The total number of APTIOM-treated patients was 992 (placebo: 418). Patients enrolled had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant Anti-Epileptic Drugs (AEDs). Overall, 69% of the patients used 2 concomitant AEDs and 28% used 1 concomitant AED. The most commonly used AEDs were carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%). Oxcarbazepine was not allowed as a concomitant AED.

During an 8-week baseline period, patients were required to have an average of ≥4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. In these 3 trials, APTIOM patients had a mean duration of epilepsy of 22 years (range 1 to 70 years) and a mean [Standard Deviation (SD)] baseline seizure frequency of 15 (22) per 28 days. Similarly, placebo patients had a mean duration of epilepsy of 22 years (range 1 to 65 years) and a mean (SD) baseline seizure frequency of 15 (18) per 28 days.

Studies 301 and 302 compared doses of APTIOM 400, 800, and 1200 mg once daily with placebo. Study 304 compared doses of APTIOM 800 and 1200 mg once daily with placebo. In all three trials,

following an 8-week Baseline Phase to establish baseline seizure frequency prior to randomization, subjects were randomized and titrated to the randomized dose. During the Titration Phase in Study 301, dosing was initiated at 400 mg once daily and increased weekly in 400 mg increments. In Study 302, in the 400 mg and 800 mg groups, dosing was initiated at 400 mg and 800 mg once daily, respectively. For the 1200 mg group, dosing was initiated at 800 mg once daily and increased to 1200 mg once daily after 2 weeks. In Study 304, for the 800 mg group, dosing was initiated at 400 mg for 2 weeks and then increased to 800 mg, and the 1200 mg group was initiated at 800 mg for 2 weeks and then increased to 1200 mg. For all 3 studies, the Titration Phase lasted 2 weeks and was followed by a Maintenance Phase that lasted 12 weeks, during which patients were to remain on a stable dose of APTIOM. Among patients randomized to and who received APTIOM in the three trials, 89% in the 400 mg dose group, 82% in the 800 mg dose group, and 71% in the 1200 mg dose group completed the studies (Placebo: 87%).

Study Results

A statistically significant decrease in median seizure frequency (from Baseline compared to the Maintenance Phase) versus placebo was observed at the 800 mg dose in Studies 301 and 302 and at the 1200 mg dose in Studies 301, 302 and 304. The proportion of responders (≥50% reduction seizure frequency) was also significantly better than placebo in both 800 and 1200 mg treatment arms in Studies 301 and 302 and in the 1200 mg treatment arm in Study 304. The efficacy of APTIOM was consistent regardless of the type of concomitant AED that was used.

Table 5. Percent Reduction in Median Seizure Frequency from Baseline to the end of the Maintenance Phase and Proportion of Patients with ≥50% Reduction in Seizure Frequency in Studies 301, 302 (mITT population), and 304 (ITT Population)

Study	AEDs + Placebo	AEDs + APTIOM (mg/day)		
		400	800	1200
Study 301				
N (mITT[3])	95	91	88	87
Median % Reduction	15.0	26.4	36.1	38.7
p-value vs. placebo[1]	-	0.31	0.01	0.01
Responder Rate (%)	18.9	24.2	33.0	42.5
p-value vs. placebo[2]	-	0.49	0.05	0.001
Study 302				
N (mITT[3])	99	94	87	81
Median % Reduction	5.6	20.7	32.6	28.2
p-value vs. placebo[1]	-	0.17	0.006	0.05
Responder Rate (%)	18.2	20.2	35.6	35.8
p-value vs. placebo[2]	-	0.86	0.01	0.01
Study 304				
N (ITT[3])	212	-	201	184
Median % Reduction	21.8	-	29.7	35.6
p-value vs. placebo[1]	-	-	0.08	0.02
Responder Rate (%)	23.1	-	30.5	42.7
p-value vs. placebo[2]	-	-	0.11	<0.0001

[1]p-value for LS mean comparisons from ANCOVA model with treatment and baseline standardized seizure frequency
[2]p-value from pairwise test of applicable group comparisons based on Chi Square test with continuity adjustment
[3]all randomized subjects with at least one dose of study medication who had at least one post-baseline seizure frequency assessment

In the baseline to treatment (i.e., titration + maintenance) period, statistically significant differences in percent reduction in median seizure frequency were observed with APTIOM 800 mg in Studies 301,

302 and 304 and APTIOM 1200 mg in Studies 301 and 304 compared to placebo. Statistically significant differences in 50% responder rates were also observed during this period with APTIOM 400 mg in Study 301, APTIOM 800 mg in Studies 301 and 302, and APTIOM 1200 mg in Studies 301, 302 and 304 compared to placebo.

There were no significant differences in seizure control as a function of gender, age or race/ethnicity although data on race were limited (19% of patients were non-Caucasian).

DETAILED PHARMACOLOGY

The precise mechanism(s) by which eslicarbazepine exerts its anticonvulsant actions are not fully characterized. *In vitro* electrophysiological studies indicate that eslicarbazepine stabilizes the inactivated state of voltage-gated sodium channels, preventing their return to the activated state resulting in an inhibition of repetitive neuronal firing. The affinity for the inactive state is 60-fold greater than the affinity for the resting state. In addition, eslicarbazepine has been shown to inhibit T-type calcium channels *in vitro* which may contribute to its anticonvulsant effects.

In vitro assays designed to detect potential secondary targets demonstrated that eslicarbazepine did not interact with any of a wide range of receptors (neurotransmitter related, ion channels, secondary messengers, growth factors/hormones, and brain/gut peptides) at clinically relevant concentrations. Eslicarbazepine does not modulate γ-aminobutyric acid (GABA) or glycine induced currents *in vitro*. *In vitro* and *in vivo* studies demonstrate that eslicarbazepine does not lead to increases in either excitatory or inhibitory neurotransmitters.

In humans, following oral administration, the pharmacological activity of APTIOM (eslicarbazepine acetate) is primarily exerted through the active metabolite eslicarbazepine.

Animal Pharmacology

Pharmacodynamics

APTIOM and eslicarbazepine demonstrate anticonvulsant effects in animal seizure models. APTIOM protects against seizures induced by bicuculline, picrotoxin, and 4-aminopyridine in mice while having no effect on those induced by N-methyl-DL-aspartate (NMDLA), kainite or strychnine. Both APTIOM and eslicarbazepine protect against electrically induced seizures and the progression of kindling in the maximum electroshock (MES) test in mice.

Pharmacokinetics

Biotransformation of APTIOM is very rapid in all animal species. Eslicarbazepine is the major metabolite in all species investigated (including humans) with the exception of the rat where oxcarbazepine is the major metabolite and concentrations of eslicarbazepine are lower. The differing species specific metabolic profiles for APTIOM following oral administration are shown below in Table 6.

Table 6. Metabolite Profile Following Oral Administration of APTIOM to Various Species

	% of Circulating Moieties that Correspond to Parent and Metabolite Following Oral Administration of SEP-0002093*			
	Eslicarbazepine Acetate	**Oxcarbazepine**	**Eslicarbazepine**	**(R)-Licarbazepine**
Human	-	1%	95%	4%
Rhesus Monkey	3%	-	97%	-
Dog	8%	4%	88%	-
Rabbit	-	7%	93%	<1%
Rat	-	86%	13%	1%
Mouse	-	25%	74%	<1%

ND = not detected

Preclinical Safety Pharmacology

The cardiovascular effects of eslicarbazepine acetate and/or its metabolites were assessed in *in vitro* and *in vivo* studies. *In vitro*, eslicarbazepine acetate and its metabolites inhibited hERG channel repolarization in transfected mammalian cells by less than 20% at the highest concentration (100 µg/mL) evaluated. In isolated canine Purkinje fibers, eslicarbazepine acetate and its metabolites at 10 and 100 µg/mL resulted in concentration related shortening of the action potential duration. The latter finding was interpreted to be related to inhibition of cardiac sodium channels in this assay. Oral administration of eslicarbazepine acetate to anesthetized dogs had no effect on cardiovascular parameters. In conscious dogs, an oral dose of 210 mg/kg produced a transient increase in heart rate as well as reduced QT and QTc intervals. No treatment-related arrhythmias or other changes in the morphology of the ECG were noted. The highest plasma concentrations of eslicarbazepine determined in the *in vivo* dog studies were lower than clinical C_{max} in anesthetized dogs and about 50% higher in conscious dogs.

Animal toxicology studies revealed no behavioral effects of eslicarbazepine acetate which would suggest abuse liability. No observations of withdrawal behaviors were noted in recovery group animals following cessation of dosing with eslicarbazepine acetate. A drug discrimination study conducted in rhesus monkeys indicated that eslicarbazepine acetate doses up to 320 mg/kg resulting in systemic exposures to eslicarbazepine comparable to those at the MRHD did not show benzodiazepine-like subjective effects.

In a study in male mice that evaluated the potential effects of abrupt termination of dosing, oral administration of eslicarbazepine acetate at dose levels of 250, 400, or 600 mg/kg/day for 21 days did not produce signs indicative of physical dependence at 250 or 400 mg/kg/day. The maximum systemic AUC-based exposure to eslicarbazepine at these doses was less than that at the maximum recommended human dose (MRHD). In the 600 mg/kg/day group, twitches/tremors and wet dog shakes were seen infrequently during the withdrawal period. Maximum exposure to eslicarbazepine at this dose was 30% higher than the MRHD.

TOXICOLOGY

The metabolism of eslicarbazepine acetate to the active moiety, eslicarbazepine, and the primary

metabolites oxcarbazepine, and (R)-licarbazepine following administration in animals varies among the species tested and in comparison to the profile seen in humans. In all nonclinical species tested, the relative exposure to oxcarbazepine (when compared to eslicarbazepine) following administration of eslicarbazepine acetate was higher than in humans, but remained a minor metabolite in rabbits and dogs. However, oxcarbazepine is the major metabolite in rats, while eslicarbazepine is the major metabolite in humans, mice, dogs, and rabbits [see Table 6, **DETAILED PHARMACOLOGY, Animal Pharmacology, Pharmacokinetics]**. Therefore the data from rat studies is considered of limited relevance to human safety assessment. Consequently carcinogenicity testing was confined to the mouse and a full set of developmental toxicology studies conducted in mice.

Single-dose Toxicity Studies

In acute toxicity studies conducted in fasted mice and rats, clinical signs indicative of neurological toxicity were hypoactivity (subdued behavior), unsteady gait/incoordination, piloerection, cold extremities, and partial closure of the eyes at oral doses in excess of 300 mg/kg in both species. Studies performed are listed in Table 7 below.

Table 7. Results of Single-Dose Toxicity Studies

Species/ Strains	Route	Dose Levels (mg/kg)	Max. Non-Lethal Dose (mg/kg)	Noteworthy Findings
Mouse/CD-1	PO	150, 300, 500	300	150 and 300 mg/kg: No noteworthy findings. 500 mg/kg: Abnormal gait, subdued behavior, partial eye closure and piloerection. 1F died. All clinical observations resolved and there were no other treatment related findings from Day 2 onwards.
Rat/S-D	PO	150, 300, 500	500	150 and 300 mg/kg: No noteworthy findings. 500 mg/kg: Abnormal gait, subdued behavior, piloerection, and cold extremities. These findings resolved. Lower weight gain in M. No other treatment related findings from Day 2 onwards.

PO: oral; M: male; F: female; h: hour; S-D: Sprague-Dawley

Repeat-dose Toxicity Studies

The majority of the nonclinical toxicity studies were conducted with eslicarbazepine acetate. However, as noted above, oxcarbazepine is the major metabolite in rats (*in vivo*), and in an effort to more fully characterize the potential toxicity of eslicarbazepine in rodents, 1-month and 3-month toxicity studies were also conducted in Wistar rats with eslicarbazepine as the test article. These data have been provided in Table 8. However, systemic exposure to eslicarbazepine at all eslicarbazepine dose levels was still below that at the MRHD and less than the exposure to oxcarbazepine.

Details of the results of repeat-dose toxicity studies in mice, rats, and dogs are provided in Table 8 below. Overall, dose limiting clinical observations were similar in all species with hypoactivity (subdued behaviour), unsteady gait/incoordination, piloerection, tremors, and prostration seen along

with decreased food consumption and reduced body weight gain. Neurological effects also included convulsions that were observed in mice and rats in safety pharmacology studies, in female mice at all dose levels in the carcinogenicity study, and in the juvenile dog study described below. The liver was the primary target organ in mice, rats, and dogs with increases in liver weights seen in all species and hepatocellular hypertrophy (rodents) or hepatocyte rarefaction (dogs) along with increases in serum total protein (rats), cholesterol (rats and dogs), and triglycerides (dogs), and an increase in plasma protein due to higher albumin and/or globulin levels (rats). In addition, haematology findings of decreased red blood cells (RBC) and/or haemoglobin (Hb) occurred in rats and prolonged activated partial thromboplastin time (APTT) was seen consistently in dogs. Clinical pathology was not conducted in mice. All findings generally occurred at systemic eslicarbazepine exposures close to or below that at the MRHD.

Table 8. Summary of Findings in Repeat-Dose Toxicity Studies

Species/Strain (Test Article)	Study Duration	Dose Range (mg/kg/day)	Noteworthy Findings (Dose levels affected)
Mouse/CD-1 (eslicarbazepine acetate)	1 and 3 months	150 to 650	Behavioural Effects (≥300 mg/kg): Subdued behaviour, piloerection, unsteady gait, irregular breathing, in-coordination, hunched posture, prostration, weight loss and tremors. Liver (≥150 mg/kg): Increased liver weight and centrilobular hypertrophy. Kidney (≥300 mg/kg): Increased kidney weight in females. Spleen (≥150 mg/kg): Increased spleen weight and/or extramedullary hemopoiesis. Body weight (≥150 mg/kg): Weight gain in F. Death (≥500 mg/kg): 4F, 2M
Rat/S-D (eslicarbazepine acetate)	2 weeks; 1, 3, and 6 months	20 to 500	Behavioural Effects (≥75 mg/kg): Subdued behaviour, piloerection, unsteady gait, partially-closed eyes, salivation, prostration, hunched posture and cold body surface. Liver (≥50 mg/kg): Increased liver weight and centrilobular hypertrophy. Effects were reversible. Kidney (≥20 mg/kg): Increased kidney weight with hyaline drop formation (males), coloured urine, increased urine volume, nephropathy. Adrenal (≥75 mg/kg): Increased adrenal weight. Thyroid (≥20 mg/kg): Follicular epithelial hypertrophy. Effects were reversible. Reproductive (≥20 mg/kg): Ovaries: prominent interstitial gland and atrophy, increased uterus weights (6-month study). Plasma Chemistry (≥20 mg/kg): Increased cholesterol total protein and globulin and decreased AST. Mildly increased ALP and ALT at ≥75 mg/kg. Effects were reversible (except cholesterol in M at 250 mg/kg). Haematology (≥20 mg/kg): Mildly decreased RBC and Hb, increased reticulocytes. Effects on RBC and Hb were reversible. Death (500 mg/kg): 4F Systemic Exposure (<500 mg/kg): Eslicarbazepine $AUC_{0\text{-}24h}$ < that at MRHD.

Species/Strain (Test Article)	Study Duration	Dose Range (mg/kg/day)	Noteworthy Findings (Dose levels affected)
Rat/Wistar (eslicarbazepine)	1 and 3 months	25 to 2000	Behavioural Effects (≥100 mg/kg): Hypoactivity, piloerection, unsteady gait, partially closed eyes, and salivation. Liver (≥75 mg/kg): Increased liver weights with centrilobular hypertrophy. At >500 mg/kg, increased incidence of enlarged and darkened livers. Thyroid (≥100 mg/kg): Epithelial hypertrophy. Kidney (≥100 mg/kg): Increased kidney weights with increased hyaline droplet formation. Ovaries (≥500 mg/kg): Prominent interstitial gland and increased corpora lutea. Plasma Chemistry (≥100 mg/kg): Increased total protein, cholesterol and bilirubin levels. Death (≥1000 mg/kg): 7M, 11F Systemic Exposure (≤1000 mg/kg): Eslicarbazepine $AUC_{0\text{-}24h}$ < that at MRHD
Dog/Beagle (eslicarbazepine acetate)	1 and 2 weeks; 1, 3, 6, and 12 months	20 to 210	Behavioural Effects (≥80 mg/kg): Emesis, unsteady gait, subdued behaviour, tremors, muscular rigidity, incoordination, impaired mobility, drowsiness, lethargy and salivation Liver (≥40 mg/kg): Increased liver weights with hepatocyte rarefaction Gall Bladder (≥40 mg/kg): Increased epithelial vacuolation and macrophage infiltration. Salivary Gland (≥160 mg/kg): Decreased serous secretion in the 3 month study only. Serum Chemistry (≥40 mg/kg): Increased cholesterol, LDH Haematology (≥40 mg/kg): Increased APTT Death (≥160 mg/kg): 1M, 1F (12 month study) Systemic Exposure (≤210 mg/kg): Eslicarbazepine $AUC_{0\text{-}24h}$ < that at MRHD

S-D: Sprague-Dawley; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APTT: activated partial thromboplastin time; RBC: red blood cells; Hb: haemoglobin; LDH: lactate dehydrogenase

Genotoxicity

In *in vitro* genotoxicity studies, eslicarbazepine acetate and the major human metabolite, eslicarbazepine, were not mutagenic in bacterial assays (Ames test) conducted in the absence and presence of rat and human liver metabolic activation systems. Eslicarbazepine acetate was weakly mutagenic in the mouse lymphoma L5178Y cell mutation test without and with metabolic activation. Eslicarbazepine acetate was clastogenic in the Chinese hamster ovary (CHO) cell cytogenetic test, but neither eslicarbazepine acetate nor eslicarbazepine was clastogenic in the chromosomal aberration assay in human peripheral blood lymphocytes. *In vivo*, eslicarbazepine acetate was not clastogenic in the mouse bone marrow micronucleus test and did not induce DNA repair (as measured by unscheduled DNA synthesis) in the mouse liver.

Carcinogenicity

In a two-year carcinogenicity study in mice, eslicarbazepine acetate was administered orally at doses of 100, 250, and 600 mg/kg/day. These doses were 0.4, 1.0, and 2.3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. An increase in the incidence of hepatocellular adenomas and carcinomas was seen at doses ≥250 mg/kg/day in males and at 600 mg/kg/day in females.

Reproduction and Development Toxicology

In a fertility study in mice, eslicarbazepine acetate was administered orally at doses of 150, 350, and 650 mg/kg/day. These doses were 0.6, 1.4, and 2.5 times the MRHD on a mg/m^2 basis. Maternal and paternal toxicity was observed at 350 and 650 mg/kg/day, respectively. A dose-related decrease in the number of implantations and number of live embryos was observed at all dose levels and in the absence of accurate counts of corpora lutea could have been the result of embryotoxicity or impairment of female or male fertility. In a study in rats at doses of 65, 125, and 250 mg/kg/day (0.5, 1.0, and 2.1 times the MRHD on a mg/m^2 basis), lengthening of estrus cycles and decreased fertility, mating performance, and pregnancy parameters (number of corpora lutea, implantations, and number of live fetuses) were seen at 250 mg/kg/day, a maternally toxic dose. Systemic exposure (AUC) to eslicarbazepine would have been less than that at the MRHD in mice at 150 and 350 mg/kg/day and in rats at all dose levels.

When eslicarbazepine acetate was administered orally at 150, 350, and 650 mg/kg/day to pregnant mice during organogenesis, maternal toxicity occurred at 350 and 650 mg/kg/day. Embryo-fetal toxicity (lower fetal weight) and increased incidences of skeletal abnormalities, including malformations, were evident at 650 mg/kg/day and potentially treatment-related increased incidences of fetal malformations were also observed at 150 and 350 mg/kg/day. Fetal growth retardation occurred at 350 and 650 mg/kg/day. Plasma eslicarbazepine exposure (C_{max} and AUC) at 150 mg/kg/day was less than that at the MRHD.

Oral administration of eslicarbazepine acetate at 40, 160, and 320 mg/kg/day to pregnant rabbits during organogenesis resulted in maternal toxicity and fetal growth retardation and increased incidences of minor skeletal abnormalities and variations at ≥160 mg/kg/day. These may reflect developmental delays. The no-effect dose (40 mg/kg/day) is less than the MRHD on a mg/m^2 basis and systemic exposure to eslicarbazepine, based on $AUC_{0\text{-}24h}$ values, was below that at the MRHD at all eslicarbazepine acetate dose levels. C_{max} after 160 and 320 mg/kg/day was slightly above and about triple, respectively, the C_{max} at the MRHD.

Oral administration of eslicarbazepine acetate to pregnant rats at 65, 125, and 250 mg/kg/day during organogenesis resulted in maternal toxicity at ≥ 125 mg/kg/day and embryo-lethality at all doses, increased incidences of skeletal variations at ≥ 125 mg/kg/day and fetal growth retardation at 250 mg/kg/day. The lowest dose tested (65 mg/kg/day) is less than the MRHD on a mg/m^2 basis and AUC-based systemic exposure to eslicarbazepine would have been less than that at the MRHD at all dose levels.

When female mice were dosed orally with eslicarbazepine acetate (150, 350, and 650 mg/kg/day) during the period of organogenesis and throughout the lactation period, body weight gain to weaning was lower and developmental delays were observed in offspring at the maternally toxic intermediate and high doses (approximately 1.4 and 2.5 times, respectively, the MRHD on a mg/m^2 basis). Systemic exposure ($AUC_{0\text{-}24h}$) to eslicarbazepine in pregnant mice at eslicarbazepine acetate dose levels up to 650 mg/kg/day was less than that at the MRHD.

When female rats were dosed orally with eslicarbazepine acetate (65, 125, and 250 mg/kg/day) during the period of organogenesis and throughout the lactation period, all doses were associated with maternal toxicity. At the high dose, a lower live birth index and lower offspring survival were seen. In addition, lower body weight gains and developmental delays were seen in intermediate and high dose offspring (approximately 1.0 and 2.1 times, respectively, the MRHD on a mg/m^2 basis). Systemic

exposure to eslicarbazepine at all eslicarbazepine acetate dose levels would be predicted to be less than that at the MRHD.

There are no clinical studies of eslicarbazepine acetate in pregnant women. Eslicarbazepine acetate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a juvenile dog study in which eslicarbazepine acetate (40, 80, and 160 mg/kg/day) was orally administered for 10 months starting on postnatal day 21, bone marrow hypocellularity and lymphoid tissue depletion observed in dead and moribund-sacrificed animals at all dose levels were considered potential evidence of immunotoxicity. Convulsions seen at the high dose were considered treatment-related, while a relationship to treatment for convulsions observed in a low dose animal late in the study was considered equivocal, since they occurred more than a day after the last dose (vs. 0.5-3.5 hours post dose at 160 mg/kg/day) and convulsions were not seen at the mid dose. Adverse effects on bone growth (decreased bone mineral content and density) were seen in females at all doses at the end of the dosing period, but not at the end of a 2-month recovery period. None of these findings were reported in young adult dogs dosed with eslicarbazepine acetate for up to 12 months in duration. A no-effect dose for adverse effects on juvenile dogs was not identified and $AUC_{0\text{-}24h}$-based exposure to eslicarbazepine was less than that at the MRHD at all eslicarbazepine acetate dose levels tested.

REFERENCES

Almeida L and Soares-da-Silva P. Eslicarbazepine acetate (BIA-2093). Neurotherapeutics. January 2007, 4:88-96.

Ben-Menachem E, Gabbai AA, Hufnagel A, Maia J, Almeida L, and Soares da Silva P. Eslicarbazepine Acetate as Adjunctive Therapy in Adult Patients with Partial Epilepsy [Study 2093-302]. Epilepsy Research. May 2010, 89 (2-3): 278-285.

Elger C, Bialer M, Cramer JA, Maia J, Almeida L, and Soares Da Silva P. Eslicarbazepine Acetate: A Double-Blind, Add-on, Placebo-Controlled Exploratory Trial in Adult Patients with Partial-Onset Seizures [Study 2093-201]. Epilepsia. March 2007, 48 (3): 497-504.

Elger C, Halasz P, Maia J, Almeida L, and 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 [Study 2093-301]. Epilepsia. 2009, 50 (3): 454-463.

Halasz P, Cramer JA, Hodoba D, Czlonkowska A, Guekht A, Maia J, Elger C, Almeida L, and Soares da Silva P. Long-Term Efficacy and Safety of Eslicarbazepine Acetate: Results of a 1- Year Open-Label Extension Study [Study 2093-301] in Partial-Onset Seizures in Adults with Epilepsy. Epilepsia. October 2010, 51 (10): 1963-1969.

Milovan D, Almeida L, Romach MK, Nunes T, Rocha JF, Sokowloska M, Sellers EM, and Soares da Silva P. Effect of Eslicarbazepine Acetate and Oxcarbazepine on Cognition and Psychomotor Function in Healthy Volunteers. Epilepsy & Behavior. August 2010, 18 (4): 366-373.

Trinka E, Ben-Menachem E, Kowacs PA, Elger C, Keller B, Loffler K, Rocha JF, and Soares da Silva P. Efficacy and Safety of Eslicarbazepine Acetate versus Controlled-release Carbamazepine Monotherapy in Newly Diagnosed Epilepsy: A Phase III Double-blind, Randomized, Parallel-group, Multicenter Study. Epilepsia. 2018, 00:1-13.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PR APTIOM®
Eslicarbazepine Acetate Tablets

Read this carefully before you start taking **APTIOM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APTIOM**.

What is APTIOM used for?
APTIOM (eslicarbazepine acetate) is a prescription medicine used to treat partial-onset seizures when taken on its own or together with other seizure medicines in adults.

How does APTIOM work?
APTIOM works in the brain to block the spread of seizure activity. The precise way that APTIOM works to treat partial-onset seizures is unknown.

What are the ingredients in APTIOM?
Medicinal ingredients: eslicarbazepine acetate
Non-medicinal ingredients: croscarmellose sodium, magnesium stearate and povidone

APTIOM comes in the following dosage forms:
Tablets: 200 mg, 400 mg, 600 mg, 800 mg

Do not use APTIOM if:
- You are allergic to the active substance (eslicarbazepine acetate), to other carboxamide derivatives (e.g., carbamazepine or oxcarbazepine which are other medicines used to treat epilepsy) or to any of the other ingredients.
- You have a certain type of heart rhythm disorder (second- or third-degree atrioventricular block).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APTIOM. Talk about any health conditions or problems you may have, including if you:
- Are taking any medicine that may have an impact on the way your heart beats; or have a condition known as PR prolongation (heart block).
- Are not sure that the medicines you are taking could have this effect, discuss this with your doctor.
- Have kidney problems. Your doctor may need to adjust the dose.
- Have liver problems.
- Have blood problems.
- Suffer from seizures that begin with a widespread electric discharge that involves both sides of the brain.
- Suffer from severe heart disease such as heart rhythm disorder, heart failure or heart attack.
- Have pacemaker problems.
- Are pregnant or planning to become pregnant. You must only take APTIOM during pregnancy if your doctor tells you to.

    - If you become pregnant while taking APTIOM, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- Are nursing or plan to nurse your baby. Do not breastfeed while you are taking APTIOM.
- Are taking oral contraceptives or other hormonal contraceptives. APTIOM may make hormonal contraceptives such as the contraceptive pill less effective. Therefore, it is recommended that you use other forms of safe and effective contraception when taking APTIOM up to the end of the current menstrual cycle after stopping treatment.
- Are taking medicines which reduce the level of sodium in your blood, e.g., diuretics.
- Are taking "statin" medicines to lower cholesterol.
- Have had a serious allergic reaction while taking carbamazepine or oxcarbazepine. If you have, you should not take APTIOM.

Other warnings you should know about:

- A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts when taking APTIOM, contact your doctor immediately.
- APTIOM may cause double vision, blurred vision, or impaired vision. If you experience visual disturbances while taking APTIOM, notify your doctor.
- APTIOM may make you feel dizzy, drowsy and affect your coordination. If this happens to you, do not drive or use any tools or machines. Take special care when taking APTIOM to avoid accidental injury (fall). Be careful until you are used to the effects this medicine might have.
- APTIOM may cause a decrease in the salt levels in your blood. This may happen especially if you take other drugs that may also decrease the salt levels in your blood. Your doctor may monitor your blood salt levels, especially if you get the following symptoms:
    - Nausea and/or vomiting
    - Feeling unwell or tired
    - Headache
    - Feeling consumed, irritated and/or alert
    - Muscle weakness or spasms
    - Increase in seizures or increase in the severity of the seizures

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APTIOM:

- Hormonal/oral contraceptives
- Other anti-epileptic drugs including carbamazepine, oxcarbazepine, phenytoin, and phenobarbital
- Medications used to lower cholesterol ("statins")
- Medications used to treat a heart condition such as beta-blocker (e.g., propranolol), and antiarrhythmics (e.g., amiodarone, verapamil) etc.

How to take APTIOM:

- Take APTIOM once a day, at about the same time every day, unless your doctor tells you otherwise. Taking APTIOM at the same time each day will have the best effect on controlling your seizures. It will also help you to remember when to take APTIOM.
- **Do not stop taking APTIOM without talking to your healthcare provider**. Stopping APTIOM suddenly can cause serious problems, including seizures that will not stop. Your doctor will decide how long you should take APTIOM for. Should your doctor decide to stop your treatment with APTIOM your dose will usually be reduced gradually.

Usual dose:

When you take APTIOM on its own:
The usual starting dose of APTIOM is 400 mg once daily. Your dose should be increased to 800 mg once daily after one or two weeks. Depending on how you respond to APTIOM, your dose may be increased to 1200 mg once daily and up to a maximum dose of 1600 mg once daily.

If you are 65 years of age or older, the recommended maximum dose is 1200 mg per day.

When you take APTIOM with other seizure medicines:
The usual starting dose of APTIOM is 400 mg once daily. Your dose should be increased to 800 mg after one or two weeks. Depending on how you respond to APTIOM, your dose may be increased to a maximum dose of 1200 mg once daily.

If you have certain kidney problems, you will be given a lower dose of APTIOM. You will be started on 400 mg every other day for two weeks followed by 400 mg once daily. Your dose may be increased to a maximum dose of 600 mg once daily.

APTIOM can be taken with or without food and the tablets can be taken whole or crushed. There are many ways to crush a tablet. For example, a mortar and pestle may be used or a store-bought tablet crusher. If you are unsure how to crush your tablets, talk with your doctor or pharmacist. Once crushed, sprinkle all the powder and pieces of the crushed tablet on applesauce or some other soft food and consume within 10 minutes, with a glass of water. The drug/food mixture should not be stored for future use.

Overdose:

If you think you have taken too much APTIOM, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose of this medication, take it as soon as you remember. If it is close to your next dose, take APTIOM at your next regular time.

What are possible side effects from using APTIOM?
These are not all the possible side effects you may feel when taking APTIOM. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.
The most common side effects associated with the use of APTIOM are:

- Dizziness
- Sleepiness/drowsiness
- Headache
- Nausea
- Double vision, blurred vision
- Vomiting
- Feeling tired/fatigue
- Poor coordination
- Shakiness

Serious Side Effects and What to do About Them				
Symptom / effect		**Talk to your Healthcare Professional**		**Seek Emergency Medical Attention**
		Only if Severe	**In all Cases**	
Unknown	Serious skin reactions (any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals)			X
	Serious allergic reactions (potential symptoms include swelling of the face, throat, hand, feet, ankles, or lower legs)			X
Rare	Thoughts of suicide or hurting yourself		X	
	Allergic reactions (potential symptoms include swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash)			X

	Decrease red and white blood cells (potential symptoms include tiredness, shortness of breath when exercising, looking pale, headache, chills, dizziness, frequent infections leading to fever, sore throat, mouth ulcers)		X	
	Decrease blood platelets (potential symptoms include bleeding or bruising more easily than normal, nose bleeds, reddish or purplish patches, or unexplained blotches on the skin)		X	
Uncommon	Cardiac arrhythmias (potential symptoms include irregular pulse, slow pulse, rapid pulse, feeling of lightheadedness, fainting, palpitations, shortness of breath)		X	
	Liver problems (symptoms like yellowing of your skin or the whites of your eyes, nausea or vomiting, loss of appetite, stomach pain, dark urine etc.)		X	
Common	Low sodium level in blood (potential symptoms include lack of energy, confusion, muscular twitching or convulsions)		X	

	Nervous system problems (symptoms like dizziness, trouble walking or with coordination, feeling sleepy and tired, trouble concentrating, vision problems etc.)		X	
	Allergic reactions that typically present with fever, rash and swollen lymph nodes, and may be associated with signs and symptoms involving other organs, e.g., liver			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to: 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 to 30°C).

Keep out of reach and sight of children.

If you want more information about APTIOM:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.sunovion.ca; or, by calling 1-866-260-6291

This leaflet was prepared by Sunovion Pharmaceuticals Canada Inc.

Last Revised: June 27, 2018