Drug Monograph

Drug/Drug Class:	**Aptiom™ (eslicarbazepine acetate) tablet/ antiepileptic**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Aptiom™ is available in 200 mg, 400 mg, 600 mg and 800 mg tablets containing 200 mg, 400 mg, 600 mg and 800 mg respectively of eslicarbazepine acetate. Sunovion Pharmaceuticals Inc. Marlborough, MA 01752 USA
Summary of Findings:	Aptiom™ is a once daily antiepileptic drug approved for adjunctive treatment of partial-onset seizures. Eslicarbazepine acetate 800 mg and 1200 mg daily significantly improved the number of seizures, the responder rate, and the number of days with seizures, compared with placebo. The most common adverse effects are dizziness, headache, somnolence, and nausea.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☒ Fiscal Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☒ 15 Day First Fill

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1]

Epilepsy affects around 2 million Americans. Partial onset seizers are one subtype that frequently leads to poor quality of life and often goes undiagnosed for an extended period of time.

Dosage Form(s) [1]

Aptiom™ is available in 200 mg, 400 mg, 600 mg and 800 mg tablets containing 200 mg, 400 mg, 600 mg and 800 mg respectively of eslicarbazepine acetate.

Manufacturer [1]

Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752 USA

Indication(s) [1]

Aptiom™ is indicated as adjunctive treatment of partial-onset seizures.

Clinical Efficacy [1-2] (mechanism of action/pharmacology, comparative efficacy)

Aptiom™ is metabolized to eslicarbazepine, an anticonvulsant whose exact mechanism of action is unknown, but which is thought to inhibit voltage-gated sodium channels.

Pharmacokinetics

	Aptiom
Protein binding	< 40%
Volume of distribution	61 L
Metabolism	Liver, extensively to eslicarbazepine (active)
Excretion	Urine (> 90%), primarily as eslicarbazepine
Half-life	13 to 20 hours

Aptiom ™ was evaluated in a pooled analysis of 3 randomized, double-blind, placebo-controlled, phase 3 clinical trials that assessed its efficacy at 3 different doses as add-on treatment in adults with partial-onset seizures. Aptiom 800 mg and 1200 mg daily significantly improved the number of seizures, the responder rate, and the number of days with seizures, compared with placebo.

PARTIAL-ONSET SEIZURES

STUDY DESIGN	A pooled analysis of 3 randomized, double-blind, placebo-controlled, phase 3 clinical trials (n=1049).
INCLUSION CRITERIA	Adults with at least a 12-month history of simple or complex partial seizures with or without secondary generalization, who were taking 1 to 3 concomitant antiepileptic drugs (AEDs) at stable dosages for at least 2 months, and who had at least 4 partial-onset seizures every 4 weeks during the 8-week baseline phase with no seizure-free interval exceeding 21 consecutive days.
EXCLUSION CRITERIA	Treatment with felbamate or oxcarbazepine.
TREATMENT REGIMEN	Patients were randomized to Aptiom 400 mg (n=195), 800 mg (n=282), 1200 mg (n=272), or placebo (n=286) once daily for 12 weeks (maintenance phase) following a 2-week titration period.
RESULTS	Mean age of patients was 37 years; mean duration of epilepsy was 22 years at baseline. The most common concomitant AEDs were carbamazepine (55% of patients or higher in any group), valproic acid (19% or higher), and lamotrigine (18% or higher). During the 12-week maintenance phase, the mean seizure frequency per 4 weeks was significantly reduced in both the Aptiom 800 mg group (6.24 +/- 0.034; 95% CI, 5.58 to 6.95) and 1200 mg group (5.95 +/- 0.035; 95% CI, 5.3 to 6.65) compared with the placebo group (8.17 +/- 0.034; 95% CI, 7.39 to 9; $p < 0.0001$ for each). The responder rate (patients with at least a 50% decrease in seizure frequency from baseline) was higher in the 800 mg group (36%) and the 1200 mg group (44%) compared with placebo (22%). The median number of days with seizures per 4 weeks was significantly reduced from baseline with Aptiom 800 mg (from 6.5 to 4.3) and 1200 mg (from 6.3 to 3.8) compared with placebo (from 5.9 to 5.3; $p < 0.01$ versus 800 mg; $p < 0.001$ versus 1200 mg). The results were consistent across subgroups, including epilepsy duration, number of concomitant AEDs (1 versus 2), and types of seizures.
SAFETY	The most common adverse effects reported in the Aptiom 800 mg group, 1200 mg group, and placebo group included dizziness (21.1%, 28.9%, and 7.3%, respectively), somnolence (13%, 15%, and 9.3%, respectively), headache (10.2%, 13.6%, and 8.7%, respectively), and nausea (7.4%, 10%, and 2.1%, respectively).

Contraindications [1]

- Hypersensitivity to eslicarbazepine acetate or oxcarbazepine

Warnings and Precautions [1]

- Abrupt discontinuation may increase seizure frequency; withdraw gradually.
- Anaphylaxis and angioedema have been reported; discontinue use if occurs.
- Dermatologic reactions, serious (eg, Stevens-Johnson syndrome), have been reported; discontinue use unless clearly not drug-related; do not initiate therapy if previous dermatologic reaction has occurred while on Aptiom or oxcarbazepine.
- Drug reaction with eosinophilia and systemic symptoms (DRESS) (ie, multiorgan hypersensitivity), potentially fatal, has been reported; discontinue and do not resume use if occurs and an alternative etiology cannot be determined; do not initiate therapy if previous DRESS has occurred while on Aptiom or oxcarbazepine.
- Hepatic injury (elevated transaminases and bilirubin) has been reported; monitoring recommended; discontinue use if jaundice or laboratory evidence of significant liver injury occurs.
- Hepatic impairment, severe; use not recommended.
- Hyponatremia has been reported; increased risk with increasing dose or concomitant hyponatremia-inducing drugs; consider monitoring; dose reduction and/or discontinuation may be necessary.
- Neurologic events, dose-dependent (eg, dizziness, gait, coordination, cognitive and visual disturbances, fatigue, and somnolence) have been reported; increased risk with large doses, during titration, elderly (60 years or older), and concomitant carbamazepine.
- Suicidal ideation and behavior have been reported with antiepileptic drugs; monitoring recommended.

Adverse Effects [1]

Most common, >= 4%	**Aptiom™ 800 mg (n=415)**	**Placebo (n=426)**
▪ Dizziness	20%	9%
▪ Headache	13%	9%
▪ Somnolence	11%	8%
▪ Nausea	10%	5%
▪ Diplopia	9%	2%
▪ Blurred vision	6%	1%
▪ Vomiting	6%	3%
▪ Ataxia	4%	2%
▪ Diarrhea	4%	3%

Drug Interactions [1]

- Antiepileptic agents: carbamazepine, phenobarbital, phenytoin, pimozide
- CYP2C19 substrates: phenytoin, clobazam, omeprazole

- CYP3A4 substrates: simvastatin
- Oral contraceptives: ethinyl estradiol, levonorgestrel
- Warfarin

Dosage and Administration [1]

The initial dose is 400 mg orally once daily for 1 week, then increase to maintenance dose of 800 mg once daily. Maximum recommended maintenance dose is 1200 mg once daily after patient tolerates 800 mg/day for at least 1 week. Alternatively, initial dose of 800 mg once daily is allowed if the need for seizure reduction outweighs increased risk of adverse reactions. Dose adjustments may be necessary for concomitant use with enzyme-inducing antiepileptic drugs or renal impairment. Gradually reduce the dose when discontinuing.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Eslicarbazepine acetate	Aptiom	Sunovion	200 mg tablets	1 tablet once daily	$449.70
			400 mg tablets	1 tablet once daily	$599.40
			600 mg tablets	1 tablet once daily	$599.40
			800 mg tablets	1 tablet once daily	$599.40

*WholesaleAcquisitionCost

Conclusion

Aptiom™ is a once daily antiepileptic drug approved for adjunctive treatment of partial-onset seizures. It was evaluated in a pooled analysis of 3 randomized, double-blind, placebo-controlled, phase 3 clinical trials that assessed efficacy at 3 different doses as add-on treatment in adults with inadequately controlled partial seizures. Aptiom 800 mg and 1200 mg daily significantly improved the number of seizures, the responder rate, and the number of days with seizures, compared with placebo. The most common adverse effects are dizziness, headache, somnolence, and nausea.

Recommendation

The Division recommends adding this drug to the current 15 day quantity limitation fiscal edit and to the current psychotropic polypharmacy clinical edit.

References

1. Product Information: Aptiom®, eslicarbazepine acetate tablets. Sunovion Pharmaceuticals Inc, Marlborough, MA, 11/2013.

2. Gil-Nagel A, Elger C, Ben-Menachem E et al: Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: integrated analysis of pooled data from double-blind phase III clinical studies. Epilepsia 2013; 54(1):98-107.

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Date: May 14, 2014

