To be sold by retail on the prescription of Neurologist only.
PRESCRIBING INFORMATION

CENOBAMATE TABLETS
CEBRIUS 12.5/25/50/100/150/200

1. Generic Name
Cenobamate Tablets 12.5 mg
Cenobamate Tablets 25 mg
Cenobamate Tablets 50 mg
Cenobamate Tablets 100 mg
Cenobamate Tablets 150 mg
Cenobamate Tablets 200 mg

2. Qualitative and quantitative composition:
Cenobamate Tablets 12.5 mg
Each Uncoated tablet contains:
Cenobamate.....12.5 mg
Excipients.....q.s.
Cenobamate Tablets 25 mg
Each film coated tablet contains:
Cenobamate.....25 mg
Excipients.....q.s.
Colours: Iron Oxide Yellow, Iron Oxide Red, Indigo carmine aluminium lake & Titanium Dioxide IP
Cenobamate Tablets 50 mg
Each film coated tablet contains:
Cenobamate.....50 mg
Excipients.....q.s.
Colours: Iron oxide Yellow & Titanium Dioxide IP
Cenobamate Tablets 100 mg
Each film coated tablet contains:
Cenobamate.....100 mg
Excipients.....q.s.
Colours: Iron Oxide Yellow, Iron Oxide Red, Indigo carmine aluminum lake & Titanium Dioxide IP

Cenobamate Tablets 150 mg
Each film coated tablet contains:
Cenobamate.....150 mg
Excipients.....q.s.
Colours: Iron Oxide Yellow, Iron Oxide Red & Titanium Dioxide IP
Cenobamate Tablets 200 mg
Each film coated tablet contains:
Cenobamate.....200 mg
Excipients.....q.s.
Colours: Iron Oxide Yellow, Iron Oxide Red & Titanium Dioxide IP

3. Dosage form and strength
Cenobamate Tablets 12.5 mg
White to off-white color round shaped biconvex Uncoated tablet plain on both sides.
Cenobamate Tablets 25 mg
Light Brown to Brown color round shaped biconvex Film coated tablet plain on both sides.
Cenobamate Tablets 50 mg
Yellow color round shaped biconvex Film coated tablets plain on both sides.
Cenobamate Tablets 100 mg
Light Brown to Brown color round shaped biconvex Film coated tablets plain on both sides.
Cenobamate Tablets 150 mg
Orange color round shaped biconvex Film coated tablets plain on both sides.
Cenobamate Tablets 200 mg
Orange color oval shaped biconvex Film coated tablets plain on both sides.

4. Clinical particulars
4.1 Therapeutic indication
It is indicated for the treatment of partial-onset seizures in adult patients.

4.2 Posology and method of administration
4.2.1 Assessments Prior to Initiating Cenobamate Tablets
Liver Function Test
Prior to initiating cenobamate tablets, obtain serum transaminases (ALT and AST) and total bilirubin, if not recently available (i.e., within 3 months), to establish baseline liver function. For patients with baseline hepatic impairment, dosage modifications are recommended.

4.2.2 Recommended Dosage
Monotherapy and Adjunctive Therapy
Cenobamate tablet is administered orally once daily with or without food. The recommended dosage and titration, which should not be exceeded because of the potential for serious adverse reactions.
Adults
The recommended starting dose of Cenobamate is 12.5 mg per day, titrated gradually to the recommended target dose of 200 mg per day. Based on clinical response, dose may be increased to a maximum of 400 mg per day.
The recommended titration schedule is provided in table 1, which should not be exceeded because of the potential for serious adverse reactions.

Table 1: Recommended Dosage for Partial-Onset Seizures in Adults

Initial Dosage	
Week 1 and 2	12.5 mg once daily
Titration Regimen	
Week 3 and 4	25 mg once daily
Week 5 and 6	50 mg once daily
Week 7 and 8	100 mg once daily
Week 9 and 10	150 mg once daily
Maintenance Dosage	
Week 11 and thereafter	200 mg once daily
Maximum Dosage	
If needed based on clinical response and tolerability, dose may be increased above 200 mg by increments of 50 mg once daily every two weeks to 400 mg.	400 mg once daily

4.2.3 Recommended Dosage in Patients with Hepatic Impairment
For patients with mild to moderate (Child-Pugh Class A to B) hepatic impairment, the maximum recommended dosage is 200 mg once daily. Cenobamate Tablet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

4.2.4 Administration Instructions
Cenobamate Tablet can be taken whole or the tablets can be crushed. The crushed tablet can be mixed with water and either administered by mouth as an oral suspension or administered via a nasogastric tube.
Administration of Crushed Tablets by Mouth as Oral Suspension
1. Crush the appropriate number of tablet(s) for the prescribed dose.
2. In a cup, combine the crushed tablet(s) and 25 mL of water.
3. Swirl to suspend the crushed tablet(s).
4. Drink the suspension immediately. Do not store the tablet-water mixture for later use.
5. To ensure no tablet residue is left in the container, rinse the container with 25 mL of water and drink.
6. Visually confirm that no particles are left in the container. If particles remain, repeat step 5.

Administration of Crushed Tablets via Nasogastric (NG) Tube
1. Crush the appropriate number of tablet(s) for the prescribed dose.
2. In an appropriate container, combine the crushed tablet(s) and 25 mL of water.
3. Swirl to suspend the crushed tablet(s).
4. Ensuring no particles are left in the container, instill the suspension with a syringe into the NG tube.
5. Refill the catheter-tip syringe again with 10 mL of water, swirl gently, and administer.
6. Visually confirm that no particles are left in the syringe. If particles remain, repeat step 5.

4.2.5 Discontinuation of Cenobamate Tablets
If Cenobamate Tablet is discontinued, the dosage should be gradually reduced over a period of at least 2 weeks, unless safety concerns require abrupt withdrawal.
4.3 Contraindications
Cenobamate Tablet is contraindicated in patients with:
Hypersensitivity to cenobamate or any of the inactive ingredients in Cenobamate Tablet. Familial Short-QT syndrome.

4.4 Special warnings and precautions for use
4.4.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking Cenobamate Tablet. DRESS has occurred, including one fatality, when Cenobamate Tablet was titrated rapidly (weekly or faster titration). No cases of DRESS were reported in an open-label safety study of 1339 partial-onset seizure patients when Cenobamate Tablet was initiated at 12.5 mg once daily and titrated every two weeks. This finding does not establish that the risk of DRESS is prevented by a slower titration; however, Cenobamate Tablet should be initiated at 12.5 mg once daily and titrated every two weeks. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, 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. This disorder is variable in its expression, and 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. Cenobamate Tablet should be discontinued immediately and not restarted if an alternative etiology for the signs or symptoms cannot be established.

4.4.2 QT Shortening
In a placebo-controlled study of the QT interval, a higher percentage of subjects who took Cenobamate Tablet (31% at 200 mg and 66% at 500 mg) had a QT shortening of greater than 20 msec compared to placebo (6-17%). Reductions of the QTc interval below 300 msec were not observed. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation. Patients with Familial Short QT syndrome should not be treated with Cenobamate Tablet. Caution should be used when administering Cenobamate Tablet and other drugs that shorten the QT interval as there may be a synergistic effect on the QT interval that would increase the QT shortening risk.
4.4.3 Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including cenobamate, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.
The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.
The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients /Incidence in Placebo Patients	Risk Differences: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for epilepsy and psychiatric indications.
Anyone considering prescribing Cenobamate Tablets or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

4.4.4 Liver Injury
Clinically significant liver injury has been reported in patients treated with Cenobamate Tablet in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic transaminases with elevated total bilirubin, have been reported after administration. Acute liver failure requiring transplantation has been reported in the postmarketing setting. Elevations of serum hepatic transaminases occurred in patients receiving Cenobamate Tablet in clinical trials. Obtain serum transaminases (ALT and AST) and total bilirubin, if not recently available (i.e., within 3 months), before initiation of Cenobamate Tablet to establish baseline liver function. Monitor for signs and symptoms of any hepatic injury during treatment, and obtain serum ALT and AST and total bilirubin promptly in patients who develop clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, jaundice, dark urine). Interrupt or discontinue treatment with Cenobamate Tablet in patients who develop liver injury without an alternative etiology.

4.4.5 Neurological Adverse Reactions
Somnolence and Fatigue
Cenobamate causes dose-dependent increases in somnolence and fatigue-related adverse reactions (somnolence, fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy). In Study 1 and Study 2, 31% of patients randomized to receive Cenobamate at 100 mg/day, 36% of patients randomized to receive Cenobamate at 200 mg/day, and 57% of patients randomized to receive Cenobamate at 400 mg/day reported at least one of these adverse reactions, compared to 19% of patients who received placebo. Somnolence and fatigue-related adverse reactions were serious in 0.4% of cenobamate-treated patients compared to no patients who received placebo and led to discontinuation in 2% of cenobamate-treated patients compared to 1% of patients who received placebo.

Dizziness and Disturbance in Gait and Coordination
Cenobamate causes dose-dependent adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, vertigo, balance disorder, ataxia, nystagmus, gait disturbance, and abnormal coordination). In Study 1 and Study 2, 21% of patients randomized to receive cenobamate at 100 mg/day, 31% of patients randomized to receive cenobamate at 200 mg/day, and 52% of patients randomized to receive cenobamate at 400 mg/day reported at least one of these adverse reactions, compared to 18% of patients who received placebo. Dizziness and disturbance in gait and coordination adverse reactions were serious in 2% of cenobamate-treated patients compared to no patients who received placebo and led to discontinuation in 5% of cenobamate-treated patients compared to 1% of patients who received placebo.

Cognitive Dysfunction

Cenobamate causes adverse reactions related to cognitive dysfunction related-events (i.e., memory impairment, disturbance in attention, amnesia, confusional state, aphasia, speech disorder, slowness of thought, disorientation, and psychomotor retardation). In Study 1 and Study 2, 6% of patients randomized to receive cenobamate at 100 mg/day, 6% of patients randomized to receive cenobamate at 200 mg/day, and 9% of patients randomized to receive cenobamate at 400 mg/day reported at least one of these adverse reactions, compared to 2% of patients who received placebo. No cognitive dysfunction-related events were serious in cenobamate-treated patients or in patients who received placebo. Cognitive dysfunction related adverse reactions led to discontinuation in 0.4% of cenobamate-treated patients compared to no patients who received placebo.

Visual Changes

Cenobamate causes adverse reactions related to visual changes including diplopia, blurred vision, and impaired vision. In Study 1 and Study 2, 9% of patients randomized to receive cenobamate at 100 mg/day, 9% of patients randomized to receive cenobamate at 200 mg/day, and 18% of patients randomized to receive cenobamate at 400 mg/day reported at least one of these adverse reactions, compared to 2% of patients who received placebo. No visual change-related events were serious in cenobamate-treated patients or in patients who received placebo. Visual change led to discontinuation in 0.5% of cenobamate-treated patients compared to no patients who received placebo.

Risk Amelioration

Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of cenobamate is known. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when cenobamate is used with other drugs with sedative properties because of potential additive effects.

4.4.6 Withdrawal of Antiepileptic Drugs
As with most antiepileptic drugs, Cenobamate Tablet should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

4.5 Drugs interactions
4.5.1 Effect of Cenobamate Tablet on Other Drugs
Table 3 summarizes the effect of Cenobamate Tablet on other drugs.
Table 3: Pharmacokinetic Drug Interactions

Drug or Substrate Type	Effect of Cenobamate Tablet on Drug or Substrate	Clinical Recommendation
Antiepileptic Drugs		
lamotrigine	↓ plasma concentrations	Because of a potential for reduced efficacy of these drugs, increase the dosage of lamotrigine or carbamazepine, as needed, when used concomitantly with Cenobamate Tablet.
carbamazepine	↓ plasma concentrations	
phenytoin	↑ plasma concentrations	Because of a potential 2-fold increase in phenytoin levels, gradually decrease phenytoin dosage by up to 50% as Cenobamate Tablet is being titrated.
phenobarbital	↑ plasma concentrations	Because of a potential for an increase in the risk of adverse reactions from these drugs, consider a reduction in dosage of phenobarbital or clobazam, as clinically appropriate, when used concomitantly with Cenobamate Tablet.
desmethylclobazam, the active metabolite of clobazam	↑ plasma concentrations	
CYP2B6 Substrates	↓ plasma concentrations	Because of a potential for reduced efficacy of these drugs, increase the dosage of CYP2B6 or CYP3A4 substrates, as needed, when used concomitantly with Cenobamate Tablet.
CYP3A Substrates	↓ plasma concentrations	
Oral contraceptives	↓ plasma concentrations	Because of the potential for reduced efficacy of oral contraceptives, women should use additional or alternative non-hormonal birth control while taking Cenobamate Tablet.
CYP2C19 Substrates	↑ plasma concentrations	Because of a potential for an increase in the risk of adverse reactions from these drugs, consider a reduction in dosage of CYP2C19 substrates, as clinically appropriate, when used concomitantly with Cenobamate Tablet.

4.5.2 Drug that Shorten the QT Interval
Cenobamate Tablet can shorten the QT interval; therefore, caution should be used when administering Cenobamate Tablet and other drugs that shorten the QT interval.

4.5.3 CNS Depressants and Alcohol
Concomitant use of Cenobamate Tablet with other CNS depressants, including alcohol, may increase the risk of neurological adverse reactions, including sedation and somnolence.

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)

4.6.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of Cenobamate Tablet in pregnant women.

In animal studies, administration of cenobamate during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (increased embryofetal mortality, decreased fetal and offspring body weights, neurobehavioral and reproductive impairment in offspring) at clinically relevant drug exposures .

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data
Animal Data
Oral administration of cenobamate (0, 10, 30, or 60 mg/kg/day) to pregnant rats during the period of organogenesis resulted in increased embryofetal mortality, reduced fetal body weights, and incomplete fetal skeletal ossification at the highest dose tested, which was associated with maternal toxicity. There was a small increase in visceral malformations at the high dose; however, teratogenic potential could not be fully evaluated because of the high rate of embryofetal deaths, which resulted in an inadequate number of fetuses examined. Maternal plasma exposure (AUC) at the no-effect dose for adverse effects on embryofetal development (30 mg/kg/day) was less than that in humans at the maximum recommended human dose (MRHD) of 400 mg.

Oral administration of cenobamate (0, 4, 12, or 36 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality at the highest dose tested, which was associated with maternal toxicity. Maternal plasma exposure at the no-effect dose (12 mg/kg/day) for adverse effects on embryofetal development was less than that in humans at the MRHD.

When cenobamate (0, 11, 22, or 44 mg/kg/day) was orally administered to female rats throughout pregnancy and lactation, neurobehavioral impairment (learning and memory deficit and increased auditory startle response) was observed in the offspring at all doses and decreased preweaning body weight gain and adverse effects on reproductive function (decreased numbers of corpora lutea, implantations, and live fetuses) were seen in the offspring at the high dose. Maternal plasma exposure at the lowest effect dose (11 mg/kg/day) for adverse effects on pre-and postnatal development was less than that in humans at the MRHD.

4.6.2 Lactation
Risk Summary
There are no data available on the presence of cenobamate in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Cenobamate was present in rat milk at concentrations similar to those in maternal plasma.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cenobamate Tablet and any potential adverse effects on the breastfed infant from Cenobamate Tablet or from the underlying maternal condition.

4.6.3 Females and Males of Reproductive Potential
Contraception
Women of reproductive potential concomitantly using oral contraceptives should use additional or alternative non-hormonal birth control.

4.6.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Juvenile Animal Toxicity Data
Cenobamate was administered orally to juvenile rats from postnatal day (PND) 7 to 70. To maintain consistent plasma drug exposures, doses were increased during the dosing period, up to 120 and 80 mg/kg/day in males and females, respectively. Adverse effects included mortality, delayed sexual maturation, neurological (decreased grip strength) and neurobehavioral (learning and memory deficits) impairment, decreased sperm count, decreased brain weight, and ocular histopathology. Recovery from these effects was observed following discontinuation of dosing. Overall, a no-effect dose for adverse effects on postnatal development was not identified. At the lowest doses tested, plasma cenobamate exposures (AUC) were less than that in humans at the maximum recommended human dose (MRHD) of 400 mg.

4.6.5 Geriatric Use
Clinical studies of Cenobamate Tablet did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of Cenobamate Tablet in the elderly population. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.6.6 Renal Impairment
Cenobamate Tablet should be used with caution and dosage reduction may be considered in patients with mild to moderate (CLcr 30 to less than 90 mL/min) and severe (CLcr less than 30 mL/min) renal impairment. Use in patients with end-stage renal disease undergoing dialysis is not recommended.

4.6.7 Hepatic Impairment
Cenobamate Tablet should be used with caution in patients with mild to moderate (5-9 points on Child-Pugh assessment; Class A or B) hepatic impairment. In these patients, the maximum recommended dosage is 200 mg once daily and additional dosage reduction may be considered. Use of Cenobamate Tablet in patients with severe (10-15 points on Child-Pugh assessment; Class C) hepatic impairment is not recommended.

4.7 Effects on ability to drive and use machines
Cenobamate Tablets has moderate influence on the ability to drive and use machines.
Cenobamate may cause somnolence, dizziness, fatigue, impaired vision and other CNS-related symptoms, which may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it is known whether cenobamate affects their ability to perform these tasks.

4.8 Undesirable effects
The following serious adverse reactions are described in more detail in the Warnings and Precautions section of the labeling:
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity *[see Warnings and Precautions]*
- QT Shortening *[see Warnings and Precautions]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions]*
- Liver Injury *[see Warnings and Precautions]*
- Neurological Adverse Reactions *[see Warnings and Precautions]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions]*

4.8.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions and for varying durations, adverse reaction frequencies observed in the clinical trials of a drug cannot be directly compared with frequencies in the clinical trials of another drug and may not reflect the frequencies observed in practice.
In all controlled and uncontrolled trials performed in adult partial-onset seizure patients, Cenobamate Tablet was administered as adjunctive therapy to 1944 patients. Of these patients, 1575 were treated for at least 6 months, 710 for at least 12 months, 349 for at least 24 months, and 320 for at least 36 months. A total of 658 patients (442 patients treated with Cenobamate Tablet and 216 patients treated with placebo) constituted the safety population in the pooled analysis of placebo-controlled studies in patients with partial-onset seizures (Studies 1 and 2). The adverse reactions presented in Table 4 are based on this safety population; the median length of treatment in these studies was 18 weeks. Of the patients in those studies, approximately 49% were male, 76% were Caucasian, and the mean age was 39 years.
In Study 1 and Study 2, adverse events occurred in 77% of patients treated with Cenobamate Tablet and 68% treated with placebo. Table 4 gives the incidence of adverse reactions that occurred in subjects with partial-onset seizures in any Cenobamate Tablet treatment group and for which the incidence was greater than placebo during the controlled clinical trials. The most common adverse reactions that occurred in Cenobamate Tablet -treated patients (incidence at least 10% and greater than placebo) were somnolence, dizziness, fatigue, diplopia, and headache.
The discontinuation rates because of adverse events were 11%, 9%, and 21% for patients randomized to receive Cenobamate Tablet at doses of 100 mg/day, 200 mg/day, and 400 mg/day, respectively, compared to 4% in patients randomized to receive placebo. The adverse reactions most commonly (1% or greater in any Cenobamate Tablet treatment group, and greater than placebo) leading to discontinuation, in descending order of frequency, were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo.

Table 4: Adverse Reactions in Pooled Placebo-Controlled Adjunctive Therapy Studies in Patients with Partial-Onset Seizures with Cenobamate Tablet Frequency in Any Treatment Arm Greater Than 1% Over Placebo

Adverse Reaction	Cenobamate tablets			Placebo
	100mg	200mg	400mg	
	n = 108 %	n= 223 %	n=111 %	n=216 %
Cardiac Disorders				
Palpitations	0	0	2	0
Ear and Labyrinth Disorders				
Vertigo	1	1	6	1
Eye Disorders				
Diplopia	6	7	15	2
Vision Blurred	2	2	4	0
Gastrointestinal Disorders				
Nausea	6	6	9	3
Constipation	2	4	8	0
Diarrhea	1	3	5	0
Vomiting	2	4	5	0
Dry Mouth	1	1	3	0
Abdominal Pain	2	2	1	0
Dyspepsia	2	2	0	0
Infections and Infestations				
Nasopharyngitis	2	4	5	3
Pharyngitis	1	2	0	0
Urinary Tract Infection	2	5	0	2
Injury, Poisoning and Procedural Complications				
Head Injury	1	0	2	0
Investigations				
AlanineAminotransferase Increased*	1	1	4	0
AspartateAminotransferase Increased	1	1	3	0
Weight Decreased	2	0	1	0
Metabolism and Nutrition Disorders				
Decreased Appetite	3	1	5	1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	4	2	5	3
Musculoskeletal Chest Pain	2	1	0	0
Nervous System Disorders				
Somnolence	19	22	37	11
Dizziness	18	22	33	15
Fatigue	12	14	24	7
Headache	10	12	10	9
Balance Disorder	3	5	9	1
Gait Disturbance	1	3	8	1
Dysarthria	2	1	7	0
Nystagmus	3	7	6	0
Ataxia	2	3	6	2
Aphasia	2	1	4	0
Asthenia	0	1	3	1
Dysgeusia	2	0	2	0
Memory Impairment	2	1	2	0
Migraine	0	0	2	0
Sedation	1	1	2	0
Tremor	0	3	1	1
Psychiatric Disorders				
Confusional State	2	2	3	0
Euphoric Mood	0	0	2	0
Irritability	1	0	2	0
Suicidal Ideation	2	1	0	0
Renal and Urinary Disorders				
Pollakiuria	0	1	0	0
Reproductive System and Breast Disorders				
Dysmenorrhea	1	2	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Hiccups	0	1	1	0
Dyspnea	0	3	0	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	2	1	0	0
Rash Papular	2	0	0	0

* Reported as an adverse reaction; see Laboratory Abnormalities for ALT changes from collected laboratory values

Laboratory Abnormalities
Hepatic Transaminases [see Warnings and Precautions]
In Study 2, there was a post-baseline elevation of alanine aminotransferase (ALT) to greater than 3 times the upper limit of normal (ULN) in 1 (0.9%) patient treated with 100 mg Cenobamate Tablets, 2 (1.8%) patients treated with 200 mg, and 3 (2.7%) patients treated with 400 mg, compared to no patients who took placebo. The maximum ALT elevation was 7.6 times ULN in patients treated with 400 mg Cenobamate Tablets.

Potassium
In clinical studies, there was a post-baseline elevation of potassium values greater than 5 meq/L (upper reference range) in patients treated with Cenobamate Tablets. In Study 1, there were 17 (17%) patients treated with Cenobamate Tablets 200 mg compared to 8 (7%) patients who took placebo with normal baseline potassium values who had at least one post-baseline maximum value greater than 5 meq/L. In Study 2, there was a dose-related distribution where at least one post-baseline potassium value was greater than 5 meq/L, occurring in 8.3%, 9.1%, and 10.8% of the patients treated with Cenobamate Tablets 100 mg, 200 mg, and 400 mg, respectively, compared to 5.6% of patients who took placebo. Two patients had a maximum potassium value of 5.9 meq/L.

Other Adverse Reactions
Gastrointestinal disorders: There was an incidence of appendicitis in the overall clinical trial safety population of 2.9 cases of appendicitis/1000 patient-years of exposure that is in excess of the expected background rate in the general population.

Adverse Reactions Based on Gender
No significant gender differences were noted in the incidence of adverse reactions.

Postmarketing Experience in United States (US)
The following adverse reactions have been identified during post approval use of cenobamate in the US. It is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Psychiatric Disorders: Psychosis (hallucinations, delusions/paranoia), hostility, aggression.
Hepatobiliary Disorders: Hepatic failure.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. For reporting suspected adverse drug reactions visit our website: https://www.intaspharma.com/adverse-event-reporting/

4.9 Overdose
There is limited clinical experience with Cenobamate Tablet overdose in humans. There is no specific antidote for overdose with Cenobamate Tablet. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation and ventilation should be ensured; monitoring of cardiac rate and rhythm and vital signs is recommended. A certified poison control center should be contacted for updated information on the management of overdose with Cenobamate Tablet. There are no data on the removal of Cenobamate Tablet using dialysis.

5. Pharmacological properties
5.1 Mechanism of Action
The precise mechanism by which cenobamate exerts its therapeutic effects in patients with partial-onset seizures is unknown. Cenobamate has been demonstrated to reduce repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel.

5.2 Pharmacodynamic properties
Interactions with Alcohol
No clinically significant differences on objective attention, psychomotor performance, and memory tests, in addition to other subjective CNS tests, were observed following concomitant use of Cenobamate Tablet and ethanol (preparation of 40% ethanol in orange juice dosed at 0.7 g/kg for males and 0.57 g/kg for females) in healthy subjects.

Cardiac electrophysiology
In a placebo-controlled QT study in healthy volunteers, dose-dependent shortening of the QTcF interval has been observed with Cenobamate Tablet [see Warnings and Precautions]. The mean ΔΔQTc is -11 [-13, -8] msec for 200 mg once daily and -18 [-22, -15] msec for 500 mg once daily (1.25 times the maximum recommended dosage). A higher percentage of Cenobamate Tablet-treated subjects (31% at 200 mg and 66% at 500 mg) had a QT shortening of greater than 20 msec compared to placebo (6-17%). Reductions of the QTc interval below 300 msec were not observed.

5.3 Pharmacokinetic properties
Cenobamate AUC increases in a greater than dose-proportional manner following single oral doses from 5 to 750 mg (0.0125 to 1.88 times the maximum recommended dosage). Cenobamate C_{max} increases in a dose proportional manner. Steady-state plasma concentrations are attained after approximately two weeks of once daily dosing.
The pharmacokinetics of cenobamate are similar when used as monotherapy or as adjunctive therapy for the treatment of partial-onset seizures, except plasma cenobamate multiple-dose exposure (C_{max}, AUC) decreased with co-administration of phenytoin by 27-28%.

Absorption
At least 88% of Cenobamate Tablet is absorbed following oral administration, with median T_{max} ranging from 1 to 4 hours.
Plasma C_{max} and AUC for Cenobamate Tablet crushed tablets mixed in water, administered either orally or through a nasogastric tube, were similar to whole tablets. The median T_{max} for crushed tablets is 0.5 hours.

Effect of Food
No clinically significant differences in cenobamate pharmacokinetics were observed following administration of a high-fat meal (800 -1000 calories with 50% fat).

Distribution
The apparent volume of distribution (Vd/F) of cenobamate after oral administration of Cenobamate Tablet is approximately 40-50 L. Plasma protein binding of cenobamate is 60% and independent of concentration *in vitro*. Cenobamate primarily binds with human albumin protein.

Elimination
The apparent terminal half-life of cenobamate is 50-60 hours and apparent oral clearance is approximately 0.45-0.63 L/hour over a dose range from 100 mg/day to 400 mg/day.

Metabolism
Cenobamate is extensively metabolized. The primary metabolic pathways are by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.

Following administration of radiolabeled cenobamate, unchanged cenobamate accounted for greater than 98% of the total AUC of radioactivity in plasma. Unchanged cenobamate accounted for 6.8% of the dose which was mainly excreted in the urine (6.4%).

Excretion
Following administration of radiolabeled cenobamate, a mean of 93.0% of the total radioactive dose was recovered in urine (87.8%) and feces (5.2%). More than 50% of the radioactivity was excreted within 72 hours of dosing.

Specific Populations
No clinically significant differences in the pharmacokinetics of cenobamate were observed based on age based on data from subjects age 18 years to 77 years, sex, or race/ethnicity based on data from subjects categorized as Asian, Black, Caucasian, Hispanic, or Other.

Patients with Renal Impairment

Cenobamate plasma AUC was 1.4 fold to 1.5 fold higher in subjects with mild (CLcr 60 to less than 90 mL/min) and moderate (CLcr 30 to less than 60 mL/min) following a single oral 200 mg dose of Cenobamate Tablet compared to healthy controls. In subjects with severe (CLcr less than 30 mL/min) renal impairment, cenobamate plasma AUC did not change significantly compared to healthy controls following single oral 100 mg dose of Cenobamate Tablet *[see Use in Specific Populations]*. The effect of hemodialysis on cenobamate pharmacokinetics has not been studied.

Patients with Hepatic Impairment
Cenobamate plasma AUC was 1.9-fold, 2.3-fold, and 4.2-fold higher in subjects with mild (5-6 points, Child-Pugh Class A), moderate (7-9 points, Child-Pugh Class B), and severe (10-15 points, Child-Pugh Class C) hepatic impairment, respectively, following a single oral 200 mg dose of Cenobamate Tablet in subjects with mild and moderate hepatic impairment and 100 mg dose of Cenobamate Tablet in subjects with severe hepatic impairment compared to matched healthy controls *[see Dosage and Administration and Use in Specific Populations]*.

Drug Interaction Studies
Clinical Studies
Alcohol
No clinically significant pharmacokinetic differences were observed for either cenobamate or alcohol when administered concomitantly.

AEDs
Multiple doses of concomitant Cenobamate Tablet 200 mg once daily increased phenytoin mean C_{max} and AUC by 70% and 84%, respectively, and phenobarbital mean C_{max} and AUC by 34% and 37%, respectively *[see Drug Interactions]*. Multiple doses of concomitant Cenobamate Tablet 200 mg once daily decreased carbamazepine mean C_{max} and AUC each by 23% *[see Drug Interactions]*.

No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with cenobamate: valproic acid, levetiracetam or lacosamide.
Based on population PK analyses, during treatment within the 100-400 mg/day Cenobamate Tablet dose range, lamotrigine concentrations are expected to decrease by 21-52% *[see Drug Interactions]*; and levetiracetam concentrations are