SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Ontozry 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg cenobamate.

Excipient with known effect

Each 100 mg film-coated tablet contains 108.7 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Film-coated round brown tablet with AV on one side and ‘100’ on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ontozry is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.

4.2 Posology and method of administration

Posology

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 (see section 4.8).

Table 1: Recommended dosage in adults with focal-onset seizures in epilepsy

Treatment phase	**Dose (per day, oral)**	**Duration**
Treatment initiation	12.5 mg	Weeks 1 and 2
	25 mg	Weeks 3 and 4
Titration	50 mg	Weeks 5 and 6
	100 mg	Weeks 7 and 8
	150 mg	Weeks 9 and 10
Target dose	200 mg	Weeks 11 and 12 and onwards
Dose optimisation	Some patients, who do not reach optimal seizure control, may benefit from doses above 200 mg (increased by increments of 50 mg/day every two weeks) up to a maximum of 400 mg daily.	

Missed doses
If patients miss one dose, it is recommended that they take a single dose as soon as they remember, unless it is less than 12 hours until their next regularly scheduled dose.

Discontinuation
It is recommended that discontinuation be undertaken gradually to minimise the potential for rebound seizures (i.e. over at least 2 weeks), unless safety concerns require abrupt withdrawal.

Elderly (65 years of age and above)
Clinical studies of cenobamate did not include sufficient numbers of subjects aged 65 and over, to determine whether they responded differently from younger patients. It has been reported that elderly subjects on antiepileptic

medicinal products have higher incidence of adverse reactions such as fatigue, gait disturbance, fall, ataxia, balance disorder, dizziness and somnolence. 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 or renal function and of concomitant disease as well as the potential interactions in polymedicated patients (see section 4.4).

Renal impairment
Cenobamate should be used with caution and reduction of the target dose may be considered in patients with mild to moderate (creatinine clearance 30 to <90 ml/min) or severe (creatinine clearance < 30 ml/min) renal impairment. The maximum recommended dose for patients with mild, moderate, or severe renal impairment is 300 mg/day. Cenobamate should not be used in patients with end-stage renal disease or patients undergoing haemodialysis.

Hepatic impairment
Exposure to cenobamate was increased in patients with chronic hepatic disease. A change in the starting dose is not required; however, a decrease in target doses of up to 50% may need to be considered. The maximum recommended dose in patients with mild and moderate hepatic impairment is 200 mg/day. Cenobamate should not be used in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of Ontozry in children aged 0 months to 18 years have not yet been established. No data are available.

Method of administration
Oral use.

Cenobamate should typically be taken once daily as single oral dose at any time. However, it should preferably be taken at the same time each day. It may be taken with or without food (see section 5.2). The tablet should be swallowed with a glass of water. The tablets cannot be split accurately as there is no break line and the accuracy of the dose cannot be ensured.
The tablet can be taken whole or can be crushed. The crushed tablet can be mixed with water and administered orally or via a nasogastric tube (see also section 6.6).

Administration of crushed tablets via nasogastric (NG) tube
Ontozry crushed tablet can be mixed with water and administered also through a nasogastric feeding tube (NG tube) as follows:

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. Shake 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Familial Short-QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products including cenobamate. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Therefore, patients should be monitored for signs of suicidal ideation and behaviours 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.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, has been reported in association with cenobamate when started at higher doses and titrated rapidly (weekly or faster titration) (see section 4.8). When cenobamate was initiated at 12.5 mg/day and titrated every two weeks, in an open-label safety study of 1,340 epilepsy patients, no cases of DRESS were reported.
At the time of prescription, patients should be advised of the signs and symptoms of DRESS and monitored closely for skin reactions. Symptoms of DRESS include typically, although not exclusively, fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. 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 signs and symptoms suggestive of these reactions appear, cenobamate should be withdrawn immediately and an alternative treatment considered (as appropriate).

QT-shortening

A dose-dependent shortening of the QTcF interval has been observed with cenobamate. Reductions of the QTcF interval below 340 msec were not

observed (see section 5.1). In clinical trials there was no evidence that the combination of cenobamate with other antiepileptic medicines led to further QT-shortening. Clinicians should use caution when prescribing cenobamate in combination with other medicinal products that are known to shorten the QT.

Familial Short QT syndrome is a rare genetic syndrome, which is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Cenobamate must not be used in patients with Familial Short-QT syndrome (see section 4.3).

Contains lactose

Patients with rare hereditary problems such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Cenobamate is extensively metabolized, primarily by glucuronidation, with oxidation contributing to a lesser degree.

Cenobamate may reduce exposures of products primarily metabolized by CYP3A4 and 2B6. Cenobamate may increase exposures of products primarily metabolized by CYP2C19. When initiating or discontinuing treatment with cenobamate or changing the dose, it may take 2 weeks to reach the new level of enzyme activity.

Pharmacodynamic interactions

CNS depressants

Concomitant use of cenobamate with other CNS depressants, including alcohol, barbiturates, and benzodiazepines may increase the risk of neurological adverse reactions. Therefore, based on individual response, doses of barbiturates and benzodiazepines may need to be reduced, as clinically appropriate, when used concomitantly with cenobamate.

Interactions with other anti-epileptic drugs

Drug type or substrate	**Clinical recommendation**	**Effect on PK parameters**
Anti-epileptic drug		
phenytoin	No dose adjustment of cenobamate is required. Phenytoin concentrations should be monitored during titration of cenobamate, and based on individual response, the dose of phenytoin may need to be	↑ phenytoin plasma concentrations In a study in healthy subjects, concomitant administration of cenobamate 200 mg/day and phenytoin 300 mg/day slightly reduced

	reduced.	cenobamate exposures (C_{max} by -27%, AUC by -28%), and increased phenytoin exposures (C_{max} by 67%, AUC by 84%).
phenobarbital	No dose adjustment of cenobamate is required. Concentrations of phenobarbital should be monitored during cenobamate titration, and based on individual response, the dose of phenobarbital may need to be reduced.	↑ phenobarbital plasma concentrations In a study in healthy subjects, concomitant administration of cenobamate 200 mg/day and phenobarbital 90 mg/day did not cause clinically meaningful changes in cenobamate exposure but led to increased phenobarbital exposures (C_{max} by 34% and AUC by 37%).
clobazam	No dose adjustment of cenobamate is required. Due to a possible increase in exposure of the active metabolite of clobazam (N-desmethylclobazam), related to the induction of CYP3A4 (formation) and the inhibition of CYP2C19 (elimination), the dose of clobazam may need to be reduced.	↑ clobazam active metabolite plasma concentrations Pharmacometric analyses of data from healthy subjects and patients predict that clobazam slightly increases cenobamate exposures (by 24%).
lamotrigine	Depending on individual response, the dose of cenobamate may need to be increased. Based on subpopulation analyses of patients taking concomitant lamotrigine, in individual cases, **higher doses (200 - 400 mg/day) of cenobamate may be required for efficacy.**	↓ lamotrigine plasma concentrations Pharmacometric analyses of data from healthy subjects and patients showed that concomitant administration of cenobamate with lamotrigine had no effect on cenobamate exposures, but resulted in dose-dependent decreases in lamotrigine concentrations (by -21%, -35%, and -52%

		for cenobamate 100, 200, and 400 mg/day).
carbamazepine	No clinically meaningful decreases in efficacy were observed in patients taking concomitant carbamazepine. No dose adjustments are required for both carbamazepine and cenobamate.	↓ carbamazepine plasma concentrations In a study in healthy subjects, concomitant administration of cenobamate 200 mg once daily and carbamazepine 200 mg twice daily showed no significant change in exposure of cenobamate, but carbamazepine exposures were slightly reduced (C_{max} reduced by 23%, AUC reduced by 24%).
Valproic acid	No dose adjustments of cenobamate or valproic acid are required.	No clinically relevant effect of valproic acid In a study in healthy subjects, concomitant administration of cenobamate 150 mg once daily and valproic acid 1,000 mg once daily showed no significant changes in exposures of either medicinal product. Pharmacometric analyses of data from healthy subjects and patients indicated that concomitant administration of cenobamate with valproic acid did not affect cenobamate exposures and had no clinically relevant reductions in valproic acid concentration.
lacosamide, levetiracetam and oxcarbazepine	No dose adjustments are required for cenobamate, lacosamide, levetiracetam, or oxcarbazepine.	No clinically relevant effect of lacosamide, levetiracetam and oxcarbazepine Pharmacometric analyses of data from healthy subjects and patients indicated that concomitant

		administration with lacosamide, levetiracetam, or oxcarbazepine did not affect the exposure of cenobamate, and cenobamate did not have a clinically relevant effect on exposures of lacosamide, levetiracetam, or oxcarbazepine.

Other medicinal products

Drug or Substrate Type	**Clinical Recommendation**	**Effect on PK parameters**
Oral contraceptives (CYP3A4)	Women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control (see section 4.6).	↓ oral contraceptives plasma concentrations Cenobamate showed a dose-dependent induction of CYP3A4, reducing exposures (AUC) of the CYP3A4 substrate, midazolam 2 mg by 72% with cenobamate 200 mg/day in healthy subjects. Since hormonal contraceptives may also be metabolized by CYP3A4, their efficacy may be reduced by concomitant use with cenobamate.
CYP3A4 substrates	An increase in the dose of medicines metabolized by CYP3A4 may be required when used concomitantly with cenobamate.	↓ CYP3A4 substrates plasma concentrations In a study in healthy subjects, concomitant administration of cenobamate 100 and 200 mg once daily reduced exposures (AUC) of the CYP3A4 substrate, midazolam 2 mg by 27% and 72%, respectively.
CYP2B6 Substrates	An increase in the dose of medicines metabolized by	↓ CYP2B6 substrates plasma concentrations

	CYP2B6 may be required when used concomitantly with cenobamate.	In a study in healthy subjects, concomitant administration of cenobamate 200 mg once daily reduced exposures of the CYP2B6 substrate, bupropion 150 mg (C_{max} reduced by 23%, AUC reduced by 39%).
CYP2C19 Substrates	A dose reduction of medicines metabolized by CYP2C19 may be required when used concomitantly with cenobamate.	↑ CYP2C19 substrates plasma concentrations In a study in healthy subjects, concomitant administration of cenobamate 200 mg once daily increased exposures of the CYP2C19 substrate, omeprazole 20 mg (C_{max} increase by 83%, AUC increased by 107%).
OAT3 substrates	Concomitant administration of cenobamate and medicinal products transported by OAT3 may result in higher exposure of these medicinal products.	↑ OAT3 substrates plasma concentrations *In vitro* studies have shown that cenobamate inhibits OAT3, a transporter predominantly involved in the elimination of certain medicines (e.g. baricitinib, cefaclor, empagliflozin, penicillin G, ritobegron, and sitagliptin).

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential and contraception in males and females
Cenobamate is not recommended in women of childbearing potential not using contraception. Women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control during treatment with cenobamate and until 4 weeks after treatment discontinuation (see section 4.5).
Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
It has been shown that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the underlying condition is responsible has not been elucidated. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Risk related to cenobamate
There are no adequate data from the use of Ontozry in pregnant women. Animal studies have shown that cenobamate crosses the placenta of rats. Studies in animals have shown reproductive toxicity at levels below clinical exposure (see section 5.3). Ontozry should not be used during pregnancy unless the clinical condition of the woman requires treatment with cenobamate. Women of childbearing potential must use effective contraception during use of cenobamate and until 4 weeks after treatment discontinuation (see section 4.5).

Breast-feeding

It is unknown whether cenobamate or its metabolites are excreted in human milk.
Studies in rats showed excretion of cenobamate in the maternal milk (see section 5.3). A risk to the suckling child cannot be excluded. As a precautionary measure, breast-feeding should be discontinued during treatment with Ontozry.

Fertility

The effects of cenobamate on human fertility are unknown. Animal data are insufficient due to exposure below clinical levels (see section 5.3).

4.7 Effects on ability to drive and use machines

Ontozry 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 (see section 4.5).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were somnolence, dizziness, fatigue and headache.

The discontinuation rates because of adverse reactions in clinical trials were 5%, 6% and 19% for patients randomised to receive cenobamate at doses of 100 mg/day, 200 mg/day and 400 mg/day respectively, compared to 3% in patients randomised to receive placebo. The 400 mg dose was more associated with adverse reactions especially when taken concomitantly with clobazam.

The adverse reactions most commonly leading to discontinuation, in descending order of frequency, were: ataxia (1.6% vs 0.5% placebo), dizziness (1.6% vs 0.5% placebo), somnolence (1.4% vs 0.5% placebo), nystagmus (0.7% vs 0 % placebo), vertigo (0.7% vs 0 % placebo) and diplopia (0.5% vs 0 % placebo). These adverse reactions are dose dependent and the titration scheme should be strictly followed).

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies are listed in table 2 per system organ class (SOC) and per frequency. Within each frequency group, undesirable effects are ranked in decreasing order of severity: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).

Table 2: Tabulated list of adverse reactions

System organ class	Frequency	Adverse reactions from clinical trials
Immune system disorders	Uncommon	Hypersensitivity*
Psychiatric disorders	Common	Confusional state, Irritability
	Uncommon	Suicidal ideation
Nervous system disorders	Very common	Somnolence*, Coordination and Gait abnormalities*, Headache
	Common	Dysarthria, Nystagmus, Aphasia, Memory impairment
Eye disorders	Common	Diplopia, Vision blurred
Gastrointestinal disorders	Common	Constipation, Diarrhoea, Nausea, Vomiting, Dry mouth
Skin and subcutaneous tissue disorder	Common	Rash*
	Rare	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Investigations	Common	Hepatic enzyme increased*

*Grouped terms: **Somnolence:** Somnolence, Fatigue, Sedation and Hypersomnia; **Coordination and Gait abnormalities**: Dizziness, Vertigo, Balance disorder, Ataxia, Gait disturbance and abnormal coordination; **Hypersensitivity**: Hypersensitivity, Drug hypersensitivity, Eyelid oedema; **Rash:** Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash pruritic; **Hepatic enzyme increased**: Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Transaminases increased.

Description of selected adverse reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Three cases of DRESS were reported within 2 to 4 weeks of starting cenobamate in studies with high starting doses (50 mg or 100 mg once daily) and weekly or faster titration. When cenobamate was initiated at 12.5 mg/day and titrated every two weeks, in an open-label safety study of 1,340 epilepsy patients, no cases of DRESS were reported.

At the time of prescription, patients should be advised of the signs and symptoms of DRESS and monitored closely for skin reactions. Symptoms of DRESS include typically, although not exclusively, fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. 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 signs and symptoms suggestive of these reactions appear, cenobamate should be withdrawn immediately and an alternative treatment considered (as appropriate). Ontozry should always be initiated at 12.5 mg once daily and titrated not faster than once every two weeks (see sections 4.2 and 4.4.).

Hypersensitivity

Four (0.9%) Cenobamate treated patients and one (0.5%) placebo patient experienced an event of hypersensitivity. Two patients in the cenobamate dose group experienced events of drug hypersensitivity. One cenobamate treated patient experienced an event of hypersensitivity and 1 cenobamate treated patient experienced an event on eyelid oedema. The placebo patient experienced an event of hypersensitivity. All events were classified as mild or moderate.

Elderly

Safety data from the Pooled Double-Blind and All Phase 2/3 datasets along with PK data from a Phase 1 study showed no additional safety risks in elderly subjects >65 years of age at study entry. Additional subgrouping by age for subjects who were >65 years of age during study participation showed similar results for adverse reactions in these 87 subjects as compared with the 51 subjects who were >65 years of age at study entry (see section 4.2).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose are expected to be consistent with the known adverse reactions of Ontozry and include somnolence, fatigue, dizziness. There is no available specific antidote to the effects of cenobamate. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX25.

Mechanism of action

Cenobamate is a small molecule with a dual mechanism of action. It is a positive allosteric modulator of subtypes of the γ-aminobutyric acid ($GABA_A$) ion channel, that does not bind to the benzodiazepine binding site. Cenobamate has also been shown to reduce repetitive neuronal firing by enhancing the inactivation of sodium channels and by inhibiting the persistent component of the sodium current. The precise mechanism of action by which cenobamate exercises its therapeutic effects in patients with focal-onset seizures is unknown.

Pharmacodynamic effects

Cardiac electrophysiology

In a placebo-controlled QT study in healthy volunteers, dose-dependent shortening of the QTcF interval has been observed with cenobamate. The mean ΔΔQTcF is -10.8 [CI: -13.4, -8.2] msec for 200 mg once daily and -18.4 [CI: -21.5, -15.2] msec for 500 mg once daily (1.25 times the maximum recommended dosage). Reductions of the QTc interval below 340 msec were not observed (see section 4.4).

Clinical efficacy and safety

The efficacy of cenobamate as adjunctive therapy in focal-onset seizures was studied in a multi-centre, randomised, double-blind, placebo-controlled study in adult patients with focal-onset epilepsy who have not been adequately controlled despite a history of treatment with anti-epileptic products. Patients were treated with one to three concomitant antiepileptic medicinal products

that remained stable over the course of double-blind study treatment. The daily dose of cenobamate ranged from 100 to 400 mg/day.
The study had an 8-week prospective baseline period, during which patients were required to have at least 3 or 4 partial-onset seizures per 28 days with no seizure-free period exceeding 3 to 4 weeks, followed by an 18-week treatment period including 12 weeks at fixed. The most commonly taken antiepileptic medicinal products at the time of study entry were levetiracetam, lamotrigine, carbamazepine and lacosamide. All subjects who entered the study continued to have seizures, despite a majority having had a history of treatment with 2 or more antiepileptic medicinal products. More than 80% of patients were taking two or more concomitant antiepileptic medicinal products at the time of study enrolment. The efficacy outcomes are summarised in table 3.
The study compared doses of cenobamate 100 mg/day, 200 mg/day and 400 mg/day with placebo, on top of standard of care. Subjects continued stable treatment on one to three background antiepileptic medicinal products. Patients were started on a daily dose of 50 mg and subsequently increased by 50 mg/day every week until 200 mg/day was reached and then increased by 100 mg/day every week in subjects randomised to 400 mg/day.
Table 3 shows the proportion of patients who exhibited a 50% or greater reduction in seizure frequency from baseline.

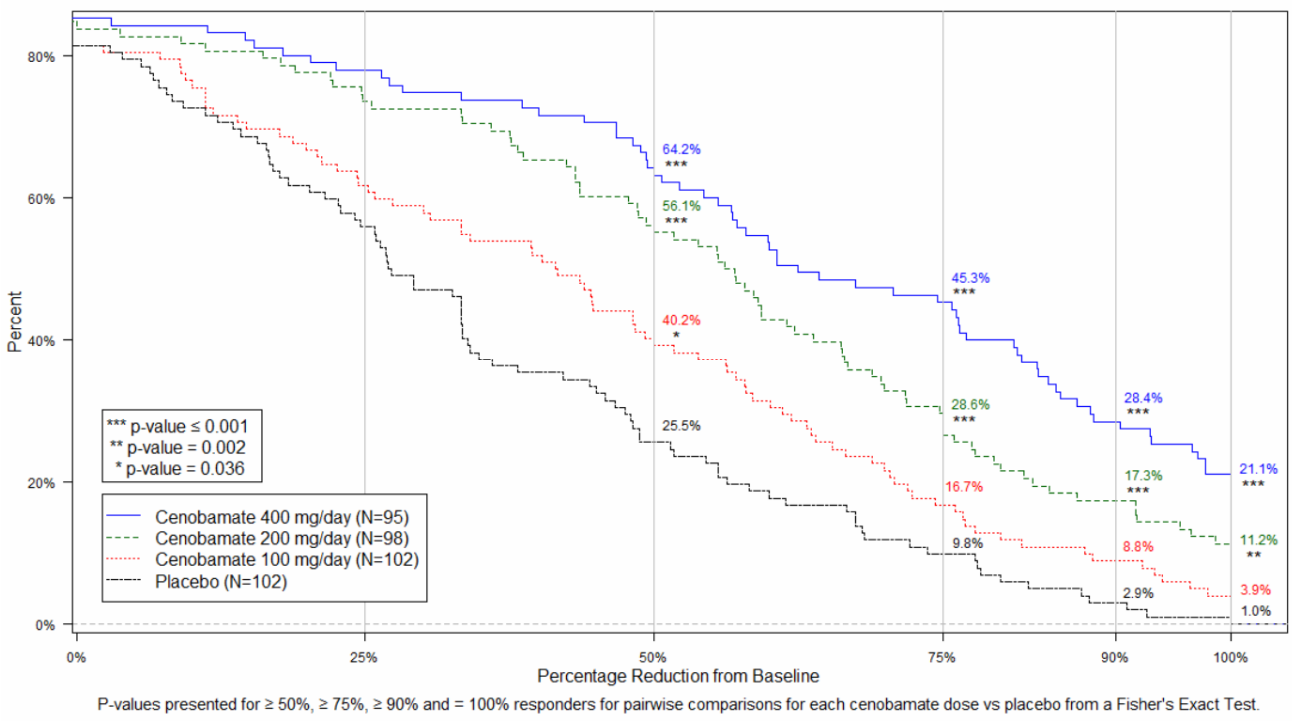
Table 3: Proportion of patients exhibiting 50% or greater response in Study C017

Study	**Standard of care and placebo**	**Standard of care and cenobamate**		
		100 mg/day	200 mg/day	400 mg/day
Study C017				
	n=102	n=102	n=98	n=95
50% Responder rate[1]	26 (25.5%)	41 (40.2%)	55 (56.1%)	61 (64.2%)
Cenobamate placebo difference		14.7% (p=0.036)	30.6% (p < 0.001)	38.7% (p < 0.001)

[1]Over 12 weeks of fixed-dose double-blind treatment

Figure 1 shows the percentage of patients by category of seizure response during the maintenance phase with increasingly stringent criteria for response.

Figure 1: Cumulative distribution of percent reduction in seizures from baseline by treatment group in the 12-week fixed-dose period in the Study



P-values presented for ≥ 50%, ≥ 75%, ≥ 90% and = 100% responders for pairwise comparisons for each cenobamate dose vs placebo from a Fisher's Exact Test.

In the study, 4 of 102 (3.9%) patients in the cenobamate 100 mg/day group, 11 of 98 (11.2%) patients in the cenobamate 200 mg/day group, 20 of 95 (21.1%) patients in the cenobamate 400 mg/day group and 1 of 102 (1%) of patients in the placebo group obtained seizure freedom (100% reduction in seizures) during the 12-week fixed-dose phase. Similar responses were seen across subpopulations greater than or less than median seizure frequency, and greater than or less than median disease duration.

Long term open label study
The majority of subjects chose to enter the open-label extension from Study 1 (98.9%). 80% of subjects remained in the study for at least 12 months, and 58% for at least 60 months. Additional seizure frequency data were collected and were consistent with the results from the double-blind portion of the study.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Ontozry in one or more subsets of the paediatric population in epilepsy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Cenobamate is well absorbed (at least 88% based on urine recovery) after oral administration, with median T_{max} ranging from 1 to 4 hours after single- or multiple-dose administration under fasted condition over the range of 10 to 400 mg.

Co-administration with a high-fat meal (800-1,000 kcal with 50% fat) showed no significant effect on the rate and the extent of absorption of cenobamate.

Plasma exposures for cenobamate crushed tablets mixed in water, administered either orally or through a nasogastric tube, were comparable to whole tablets (confidence intervals for AUC and C_{max} within 80-125%). The median T_{max} for crushed tablets is 0.5 hours.

Distribution

The apparent volume of distribution (Vd/F) of cenobamate after oral administration 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.

Biotransformation

Cenobamate is extensively metabolised. The primary metabolic pathway is glucuronidation via UGT2B7 and to a lesser extent by UGT2B4. Minor pathways for metabolism of cenobamate include oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.

Elimination

Cenobamate and its metabolites are eliminated primarily via urine. Excretion via faeces accounted for only 5.2% of the dose. More than 50% of the dose was excreted within 72 hours. The apparent terminal half-life of cenobamate in plasma was 50-60 hours within the therapeutic range of 100 mg/day to 400 mg/day. Steady state is reached by 14 days.

Linearity/non-linearity

The C_{max} of cenobamate increased proportionally with increasing doses following single oral doses from 5 to 750 mg and multiple oral doses from 50 to 500 mg/day. Steady-state exposures (C_{max} and AUC) increased proportionally with increasing doses in the therapeutic range (100 to 400 mg), but doses less than 100 mg/day may be cleared faster.

Special populations

Renal impairment

Cenobamate plasma AUC was 1.4-fold to 1.5-fold higher in subjects with mild (CL_{cr} 60 to < 90 mL/min) and moderate (CL_{cr} 30 to < 60 mL/min) renal impairment following a single oral 200 mg dose of cenobamate compared to healthy controls. In subjects with severe (CL_{cr} < 30 mL/min) renal impairment, cenobamate plasma AUC did not change significantly compared to healthy controls following single oral 100 mg dose of cenobamate (see section 4.2), The effect of haemodialysis on cenobamate pharmacokinetics has not been studied.

Hepatic impairment

Cenobamate plasma AUC was 1.9-fold and 2.3-fold higher in subjects with mild and moderate hepatic impairment, respectively, following a single oral 200 mg dose of cenobamate compared to matched healthy controls (see section 4.2). The effect of severe hepatic impairment on cenobamate pharmacokinetics has not been studied.

Gender

There was no difference observed in the pharmacokinetics of cenobamate between male and female patients.

Ethnicity
No clinically significant effect of ethnicity on the pharmacokinetics of cenobamate was noted in a population PK analysis of pooled data from clinical studies from subjects categorised as Asian, Black, Caucasian, Hispanic or other.

Body weight
A 45% decrease in exposure has been estimated across a body weight range from 54 kg to 112 kg. This variability is not considered to be clinically relevant when establishing a dose of cenobamate. However, cenobamate dose adjustments may need to be considered in patients who experience weight changes of ≥30% of their initial body weight, or more.

Elderly (65 years and above)
No clinically significant differences in the pharmacokinetics of cenobamate were observed based on age based on data from subjects aged 18 years to 77 years.

Paediatric population
Safety and effectiveness of Ontozry in patients less than 18 years of age has not been established.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential. However, maximum systemic exposure achieved in the carcinogenicity study in rats was less than that in humans at the maximum recommended human dose (MRHD) of 400 mg/day.

Repeated dose toxicity
Maximum doses in repeat dose toxicity studies were limited by the exaggerated CNS effects of cenobamate (including hypoactivity, uncoordinated gait, hypothermia, and tremor). Systemic exposures at NOAEL (no observed adverse effect levels) were similar to or below exposures reached in humans at the MRHD.

Toxicity to reproduction and development
Reproductive toxicity studies with once daily oral administration showed adverse effects on embryo-foetal and postnatal development. No adverse effects were observed on fertility in a dedicated study in rats. However, systemic exposures at the respective NOAELs for the fertility, embryo-foetal development, pre- and postnatal development studies were below human exposure at the MRHD.

Cenobamate did not show any teratogenic effects when orally administered twice daily to female rats and once daily to female rabbits, during the period of organogenesis. However, administration of cenobamate to pregnant rabbits resulted in increased embryo-foetal mortality, at a dose level associated with maternal toxicity. The systemic exposure at the respective NOELs (no observed effect levels) was below human exposure at the MRHD.

When cenobamate was administered to female rats throughout pregnancy and lactation, neurobehavioural impairment (increased auditory startle response) was observed in the offspring at all doses and decreased preweaning body weight gain and adverse reactions on female reproductive function (decreased numbers of corpora lutea, implantations and live foetuses) were seen in the offspring.

Placental and lacteal transfer of cenobamate was confirmed by the presence of cenobamate in both amniotic fluid and foetal blood from pregnant rats and in the milk of lactating rats.

The environmental risk assessment demonstrated that cenobamate is very persistent (vP) in aquatic systems (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content

lactose monohydrate
magnesium stearate (E470b)
microcrystalline cellulose (E460)
silica, colloidal anhydrous (E551)
sodium starch glycolate

Film-coating

indigo carmine aluminium lake (E132)
iron oxide red (E172)
iron oxide yellow (E172)
macrogol
partially hydrolysed poly(vinyl alcohol) (E1203)
talc (E553b)
titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister pack containing 14, 28 or 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Cenobamate is very persistent (vP) in aquatic systems. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The crushed tablet can also be administered via a nasogastric feeding tube (NG), in this case the tablet can be crushed to a powder and mixed with water (25 ml).
Refer to section 4.2 for detailed information on administration through a nasogastric tube.

7 MARKETING AUTHORISATION HOLDER

Angelini Pharma UK-I Limited
6th Floor, Napier House
24 High Holborn
London
WC1V 6AZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 56215/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/01/2026

10 DATE OF REVISION OF THE TEXT

15/04/2025