

ANNEX I

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 12.5 mg tablets
Ontozry 25 mg film-coated tablets
Ontozry 50 mg film-coated tablets
Ontozry 100 mg film-coated tablets
Ontozry 150 mg film-coated tablets
Ontozry 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ontozry 12.5 mg tablets

Each tablet contains 12.5 mg cenobamate.

Ontozry 25 mg film-coated tablets

Each film-coated tablet contains 25 mg cenobamate.

Ontozry 50 mg film-coated tablets

Each film-coated tablet contains 50 mg cenobamate.

Ontozry 100 mg film-coated tablets

Each film-coated tablet contains 100 mg cenobamate.

Ontozry 150 mg film-coated tablets

Each film-coated tablet contains 150 mg cenobamate.

Ontozry 200 mg film-coated tablets

Each film-coated tablet contains 200 mg cenobamate.

Excipient with known effect

Each 12.5 mg tablet contains 39.7 mg lactose monohydrate.
Each 25 mg film-coated tablet contains 79.3 mg lactose monohydrate.
Each 50 mg film-coated tablet contains 158.7 mg lactose monohydrate.
Each 100 mg film-coated tablet contains 108.7 mg lactose monohydrate.
Each 150 mg film-coated tablet contains 163 mg lactose monohydrate.
Each 200 mg film-coated tablet contains 217.4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ontozry 12.5 mg tablet

Tablet

Ontozry 25 mg, 50 mg, 100 mg, 150 mg and 200 mg film-coated tablet

Film-coated tablet

Ontozry 12.5 mg tablet

Uncoated round white to off-white tablet with AV on one side and '12' on the other side

Ontozry 25 mg film-coated tablet

Film-coated round brown tablet with AV on one side and '25' on the other side

Ontozry 50 mg film-coated tablet

Film-coated round yellow tablet with AV on one side and '50' on the other side

Ontozry 100 mg film-coated tablet

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

Ontozry 150 mg film-coated tablet

Film-coated light orange round tablet with AV on one side and '150' on the other side

Ontozry 200 mg film-coated tablet

Film-coated oval, light orange tablet with AV on one side and '200' 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 a history of 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.

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 in several indications. 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, and the available data do not exclude the possibility of an increased risk for cenobamate. 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 antiepileptics

Phenytoin

In a study in healthy subjects, concomitant administration of cenobamate 200 mg/day and phenytoin 300 mg/day slightly reduced cenobamate exposures (C_{\max} by -27%, AUC by -28%), and increased phenytoin exposures (C_{\max} by 67%, AUC by 84%). 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 reduced.

Phenobarbital

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%). 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.

Clobazam

Pharmacometric analyses of data from healthy subjects and patients predict that clobazam slightly increases cenobamate exposures (by 24%). No dose adjustment of cenobamate is required.

Due to a possible increase in exposure of the active metabolite of clobazam (N-desmethyloclobazam), related to the induction of CYP3A4 (formation) and the inhibition of CYP2C19 (elimination), the dose of clobazam may need to be reduced.

Lamotrigine

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). Based on subpopulation analyses of patients taking concomitant lamotrigine, higher doses (200 - 400 mg/day) of cenobamate may be required for efficacy when co-administered with lamotrigine. Depending on individual response, the dose of cenobamate may need to be increased.

Carbamazepine

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%). No clinically meaningful decreases in efficacy were observed in subpopulation analyses of patients taking concomitant carbamazepine. Therefore, no dose adjustments are required.

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. No dose adjustments are required.

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. No dose adjustments are required for cenobamate, lacosamide, levetiracetam, or oxcarbazepine.

Other medicinal products

Oral contraceptives

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. Therefore, women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control (see section 4.6).

CYP3A4 substrates

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. An increase in the dose of medicines metabolized by CYP3A4 may be required when used concomitantly with cenobamate.

CYP2B6 substrates

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%). An increase in the dose of medicines metabolized by CYP2B6 may be required when used concomitantly with cenobamate.

CYP2C19 substrates

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%). A dose reduction of medicines metabolized by CYP2C19 may be required when used concomitantly with cenobamate.

OAT3 substrates

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). Therefore, concomitant administration of cenobamate and medicinal products transported by OAT3 may result in higher exposure of these medicinal products.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ 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
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 national reporting system listed in [Appendix V](#).

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 $\Delta\Delta$ QTcF 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.

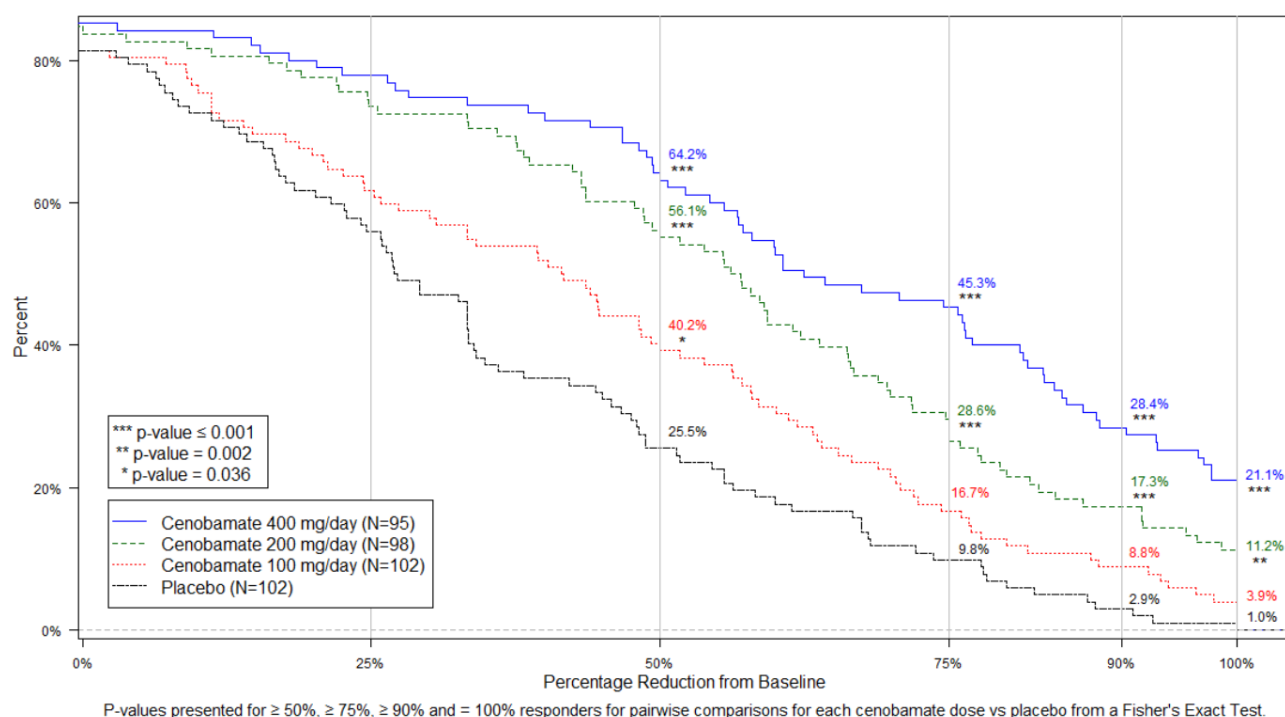
Table 3: Proportion of patients exhibiting 50% or greater response in Study C017

Table 5: 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)

¹Over 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



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.

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 $\geq 30\%$ 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 and film-coated tablet content

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

Film-coating

25 mg and 100 mg film-coated tablets

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)

50 mg film-coated tablets

iron oxide yellow (E172)

macrogol

partially hydrolysed poly(vinyl alcohol) (E1203)

talc (E553b)

titanium dioxide (171)

150 mg and 200 mg film-coated tablets

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 blisters

Ontozry Treatment Initiation pack 12.5 mg tablets and 25 mg film-coated tablets

Pack of 14 tablets of 12.5 mg and 14 film-coated tablets of 25 mg

Ontozry 50 mg film-coated tablets

50 mg – packs of 14, 28 or 84

Ontozry 100 mg film-coated tablets

100 mg – packs of 14, 28 or 84

Ontozry 150 mg film-coated tablets

150 mg – packs of 14, 28 or 84

Ontozry 200 mg film-coated tablets

200 mg – packs of 14, 28 or 84

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.

7. MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome – Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/001
EU/1/21/1530/002
EU/1/21/1530/003
EU/1/21/1530/004
EU/1/21/1530/005
EU/1/21/1530/006
EU/1/21/1530/007
EU/1/21/1530/008
EU/1/21/1530/009
EU/1/21/1530/010
EU/1/21/1530/011
EU/1/21/1530/012
EU/1/21/1530/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26/03/2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE ACTIVE SUBSTANCE AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the active substance

SK Biotek Co., Ltd
Daejeon Plant
325, Expore,
Yuseong-gu, Daejeon, 34124
Republic of Korea

Name and address of the manufacturer responsible for batch release

Swiss Caps GmbH
Grassingerstrasse 9
83043 Bad Aibling
Germany

Aziende Chimiche Riunite Angelini Francesco ACRAF SPA
Via Vecchia del Pinocchio, 22 60100
Ancona (AN), Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON – TREATMENT INITIATION PACK****1. NAME OF THE MEDICINAL PRODUCT**

Ontozry 12.5 mg tablets
Ontozry 25 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 12.5 mg tablet contains 12.5 mg cenobamate.
Each 25 mg film-coated tablet contains 25 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Treatment initiation pack
Each pack of 28 tablets for a 4-week treatment schedule contains:
14 tablets of 12.5 mg
14 film-coated tablets of 25 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/001 14 tablets of 12.5 mg and 14 film-coated tablets of 25 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ontozry 12.5 mg, Ontozry 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON INCLUDED IN THE TREATMENT INITIATION PACK

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 12.5 mg tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Weeks 1 and 2

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/001 14 tablets of 12.5 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ontozry 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER – TREATMENT INITIATION PACK
--

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 12.5 mg tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON INCLUDED IN THE TREATMENT INITIATION PACK

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 25 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Weeks 3 and 4

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/001 14 film-coated tablets of 25 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Ontozry 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 25 mg film-coated tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Ontozry 50 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/002	14 film-coated tablets of 50 mg
EU/1/21/1530/003	28 film-coated tablets of 50 mg
EU/1/21/1530/004	84 film-coated tablets of 50 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ontozry 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 50 mg film-coated tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Ontozry 100 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/005	14 film-coated tablets of 100 mg
EU/1/21/1530/006	28 film-coated tablets of 100 mg
EU/1/21/1530/007	84 film-coated tablets of 100 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ontozry 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 100 mg film-coated tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Ontozry 150 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/008	14 film-coated tablets of 150 mg
EU/1/21/1530/009	28 film-coated tablets of 150 mg
EU/1/21/1530/010	84 film-coated tablets of 150 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ontozry 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 150 mg film-coated tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Ontozry 200 mg film-coated tablets
cenobamate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg cenobamate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1530/011	14 film-coated tablets of 200 mg
EU/1/21/1530/012	28 film-coated tablets of 200 mg
EU/1/21/1530/013	84 film-coated tablets of 200 mg

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ontozry 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ontozry 200 mg film-coated tablets
cenobamate

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Angelini Pharma S.p.A (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ontozry 12.5 mg tablets
Ontozry 25 mg film-coated tablets
Ontozry 50 mg film-coated tablets
Ontozry 100 mg film-coated tablets
Ontozry 150 mg film-coated tablets
Ontozry 200 mg film-coated tablets
cenobamate

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ontozry is and what it is used for
2. What you need to know before you take Ontozry
3. How to take Ontozry
4. Possible side effects
5. How to store Ontozry
6. Contents of the pack and other information

1. What Ontozry is and what it is used for

Ontozry contains the active substance cenobamate. It belongs to a group of medicines called 'anti-epileptics'. These medicines are used to treat epilepsy, a condition where someone has seizures or fits because of abnormal activity in the brain.

Ontozry is used in combination with other antiepileptic medicines in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products, to treat a type of epilepsy that has focal-onset seizures with or without secondary generalisation. Focal-onset seizures are those caused by abnormal brain activity starting in a part of the brain on one side, and secondary generalisation means that the abnormal activity is spreading to both sides of the brain. The medicine can be used only in adults.

2. What you need to know before you take Ontozry

Do not take Ontozry

- **if you are allergic** to cenobamate or any of the other ingredients of this medicine (listed in section 6).
- you were born with heart problems, with changes in the electrical activity of the heart, related to a rare condition called familial short-QT syndrome.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ontozry or during treatment if:

- you have thoughts of harming or killing yourself. A few people being treated with anti-epileptic medicines such as Ontozry have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, contact your doctor immediately.
- you have a serious skin reaction which may include high temperature and other flu-like symptoms, rash on the face, rash spreading to other parts of the body, swollen glands (enlarged lymph nodes); and blood tests showing increased levels of liver enzymes and of a type of white blood cell (eosinophilia).
-

Children and adolescents

Ontozry is not recommended in children and adolescents under 18 years, as it was not investigated in this group.

Other medicines and Ontozry

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Taking Ontozry with certain other medicines may affect how the other medicines work or how Ontozry works. Do not start or stop other medicines without talking to your doctor or pharmacist.

Tell your doctor if you are taking any of the following medicines, as your dose may need to be adjusted:

- medicines used to help you fall asleep such as barbiturates and benzodiazepines.
- other medicines to treat epilepsy, such as clobazam, phenytoin and phenobarbital, lamotrigine.
- birth control medicines (oral contraceptives) as these may be less effective when combined with Ontozry. Your doctor may prescribe alternative methods for preventing pregnancy while you take this medicine and up to 4 weeks after you stop taking this medicine.
- medicines, which are known to be transformed in the body by specific groups of enzymes such as midazolam (a medicine used to stop prolonged, acute (sudden) convulsive seizures, for sedation and sleep problem), bupropion (a medicine used to help stop smoking), omeprazole (a medicine used to treat heartburn or stomach ulcer), baricitinib (a medicine used to treat painful inflammation of the joints or skin eczema), cefaclor (an antibiotic), empagliflozin (a medicine used to treat high blood glucose in diabetes), penicillin G (an antibiotic), ritobegron (a medicine used to treat overactive bladder), sitagliptin (a medicine used to control high blood glucose in diabetes).

Ontozry with alcohol

Do not take this medicine with alcohol. Ontozry can increase the effects of alcohol such as feeling tired or sleepy and you should not drink alcohol with this medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before you take this medicine.

Only take Ontozry during pregnancy if you and your doctor decide that it is absolutely necessary. You must use effective contraception during use of cenobamate and until 4 weeks after you stop taking this medicine. Ask your doctor for advice regarding effective measures of birth control.

You should stop breast-feeding while taking Ontozry.

Driving and using machines

- You may feel sleepy, dizzy or tired, and your vision may be reduced while taking Ontozry.

- These effects are more likely at the start of the treatment or after your dose is increased.
- Do not drive, cycle or use any tools or machines if your reaction are slowed down and until you know how the medicine affects you.

Ontozry contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, speak with your doctor before taking this medicine.

3. How to take Ontozry

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You will take Ontozry with other medicines to treat epilepsy.

The recommended dose is

You will start Ontozry with a daily dose of one 12.5 mg tablet for the first 2 weeks, followed by one 25 mg tablet once a day for the next 2 weeks. Then your dose will be gradually adjusted every 2 weeks until you reach the dose that works best. Your doctor will work out the right daily dose for you and may need to adjust it over time.

The recommended daily dose is between 200 mg and 400 mg once daily.

Method of use

Take the recommended dose once a day at around the same time. You can take Ontozry at any time either during the day or in the evening, with food or between meals.

Swallow the tablets whole with a glass of water. Do not break the tablets in half because the tablets are not suitable for splitting into two equal halves.

If you take more Ontozry than you should

Talk to your doctor. You may feel dizzy, tired and sleepy.

If you forget to take Ontozry

Take the forgotten dose as soon as you remember, if fewer than 12 hours have passed since you should have taken it. If more than 12 hours have passed, skip the forgotten dose and take the next dose at your regular time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Ontozry

Do not reduce the dose or stop taking Ontozry without checking with your doctor. Your doctor will explain how to stop taking Ontozry by reducing the dose gradually.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have any of the following serious side effects:

Rare side effects (may affect up to 1 in 1,000 people):

- a serious skin reaction which may include fever and other flu-like symptoms, a rash on the face, rash spreading to other areas of the body, and swollen glands (enlarged lymph nodes). Blood

tests may show increased levels of liver enzymes and of a type of white blood cell (eosinophilia).

You may get the following other side effects with this medicine. Tell the doctor if you have any of the following:

Very common side effects (may affect more than 1 in 10 people):

- feeling sleepy (somnolence), sedated or very tired (fatigue)
- feeling dizzy
- spinning sensation (vertigo)
- having problems with coordination of movements, having problems walking or keeping your balance (ataxia, gait disturbance, abnormal coordination)
- headache

Common side effects (may affect up to 1 in 10 people):

- reduced memory, confusion
- excitability
- having difficulty in saying words or difficulty speaking
- rapid and uncontrollable movements of the eyes (nystagmus), blurred vision, double vision
- nausea (feeling sick), vomiting, constipation or diarrhoea
- dry mouth
- rash, itching
- swollen eyelids, swollen limbs
- blood tests showing increases in levels of certain liver enzymes

Uncommon side effects (may affect up to 1 in 100 people):

- allergic reactions

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ontozry

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ontozry contains

- The active substance is cenobamate.
One Ontozry 12.5 mg tablet contains 12.5 mg cenobamate.
One Ontozry 25 mg film-coated tablet contains 25 mg cenobamate.
One 50 mg film-coated tablet contains 50 mg cenobamate.
One 100 mg film-coated tablet contains 100 mg cenobamate.
One 150 mg film-coated tablet contains 150 mg cenobamate.

- One 200 mg film-coated tablet contains 200 mg cenobamate.
- The other ingredients are microcrystalline cellulose (E460), lactose monohydrate, sodium starch glycolate, silica colloidal anhydrous (E551), magnesium stearate (E470b)

25 mg and 100 mg film-coated tablets: 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)

50 mg film-coated tablets: iron oxide yellow (E172), macrogol, partially hydrolysed poly(vinyl alcohol) (E1203), talc, titanium dioxide (171)

150 mg and 200 mg film-coated tablets: iron oxide red (E172), iron oxide yellow (E172), macrogol, partially hydrolysed poly(vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171)

What Ontozry looks like and contents of the pack

Ontozry 12.5 mg are uncoated round white to off-white tablets with AV on one side and '12' on the other side.

Ontozry 25 mg are round brown film-coated tablets with AV on one side and '25' on the other side.

Ontozry 50 mg are round yellow film-coated tablets with AV on one side and '50' on the other side.

Ontozry 100 mg are round brown film-coated tablets with AV on one side and '100' on the other side.

Ontozry 150 mg are round light orange film-coated tablets with AV on one side and '150' on the other side.

Ontozry 200 mg are oval light orange film-coated tablets with AV on one side and '200' on the other side.

Ontozry Treatment Initiation pack contains 14 tablets of 12.5 mg and 14 film-coated tablets of 25 mg.

Ontozry 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets are available in packs of 14, 28 or 84.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Angelini Pharma S.p.A
Viale Amelia 70, 00181
Rome – Italy

Manufacturer

Swiss Caps GmbH
Grassingerstrasse 9
83043 Bad Aibling
Germany

Aziende Chimiche Riunite Angelini Francesco ACRAF SPA
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Ancona (AN), Italy

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.