Date: 22 July 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ONTOZRY

International non-proprietary name: cenobamate

Pharmaceutical form: tablets, film-coated tablets

Dosage strength(s):

tablets: 12.5 mg

film-coated tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Arvelle Therapeutics International GmbH

Marketing Authorisation No.: 68051

Decision and Decision date: approved on 19 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
FT-IR	Fourier-transform infrared
GC	Gas chromatography
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
KF	Karl Fischer
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
PVC	Polyvinyl chloride
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance cenobamate of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Ontozry is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy, which are not adequately controlled despite prior treatment with at least two anti-epileptic medicinal products.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
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, the dose may be increased to a maximum of 400 mg per day.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 February 2021
Formal control completed	19 February 2021
List of Questions (LoQ)	27 May 2021
Answers to LoQ	5 August 2021
Predecision	2 November 2021
Answers to Predecision	22 December 2021
Labelling corrections	22 February 2022
Answers to Labelling corrections	23 March 2022
Final Decision	19 May 2022
Decision	approval

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3 Medical Context

Epilepsy affects about 70 million people worldwide, making it one of the most prevalent serious neurological conditions. Each year, 16 to 134 new-onset epilepsy cases per 100,000 people are diagnosed (Laxer 2014). In Europe, age-adjusted prevalence has been reported to range from 2.7 in Italy to 5.5 per 1,000 in Denmark and 7.0 per 1,000 in European regions of Turkey. Age adjusted incidence of epilepsy in European studies ranges from 26 per 100,000 person-years in Norway to 47 per 100,000 person-years in England. Epilepsy has been noted to be the most common serious neurological disorder in the UK (Banerjee 2009, National Clinical Guideline Centre 2012).

The International League Against Epilepsy (ILAE) accepted recommendations to define epilepsy as a disease of the brain, defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (≥60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher 2014).

Epilepsy has numerous causes, each reflecting underlying, genetic or acquired brain dysfunction (Stafstrom 2015). Approximately 75% of epilepsy begins during childhood (Stafstrom 2015). People with epilepsy have a poorer overall health status, impaired intellectual and physical functioning, are at greater risk of accidents and injuries and may suffer negative side effects from anti-seizure medications. They have a high rate of comorbidities, including somatic, behavioural and psychiatric disorders (Neligan 2011, Stafstrom 2015).
The risk of premature mortality is 1.6 to 3 times higher in people with epilepsy than in the general population (Thurman 2017). Mortality may be due to sudden unexpected death in epilepsy (SUDEP), fatal status epilepticus, an increased risk of dying from injuries such as drowning or falls, suicide or non-psychiatric comorbidities including neoplasia and cerebrovascular and respiratory disease (Neligan 2011; Thurman 2017). However, epilepsy-related death seems to be avoidable to some extent because the greater risk of death over the general population is greatly reduced by achieving seizure freedom through establishing effective treatment strategies (Neligan 2009; Neligan 2011).

Cenobamate is a novel tetrazole-derived compound with one chiral centre. Like a BCS Class 1 drug, it shows high solubility and high permeability. Cenobamate is a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel, via a binding site different from that of benzodiazepines. It has been proposed that cenobamate enhances the presynaptic release of GABA, thereby increasing inhibitory GABAergic neurotransmission. 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 mechanism of action by which cenobamate exercises its therapeutic effects remains to be fully elucidated.

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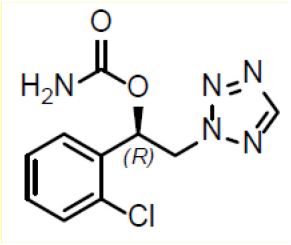
4 Quality Aspects

4.1 Drug Substance

INN: Cenobamate
Chemical name: [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate
Molecular formula: $C_{10}H_{10}ClN_5O_2$
Molecular mass: 267.67 g/mol
Molecular structure:



Cenobamate is a white to off-white powder which is non-hygroscopic and soluble to freely soluble in organic solvents. It has one stereogenic centre and is synthesised as the *R*-isomer.

The drug substance exhibits polymorphism. Cenobamate is consistently produced as a single crystalline form.

The synthesis of the drug substance has been adequately described and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

The drug substance specification includes tests for description (visual), identification (FT-IR, HPLC), chiral purity (HPLC), chemical purity (HPLC), related substances (HPLC), assay (HPLC), water content (KF), sulphated ash (Ph. Eur.), residual solvents (GC) and particle size distribution (laser diffraction). The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent drug substance quality.

The bulk drug substance is packaged in an appropriate container closure system. Stability data have been presented indicating that the drug substance is sufficiently stable.

4.2 Drug Product

Ontozry is presented as immediate release tablets of six dosage strengths: uncoated tablets (12.5 mg) and film-coated tablets (25 mg, 50 mg, 100 mg, 150 mg and 200 mg). The dosage strengths are mainly distinguishable by colour, size and debossing.

The composition of the drug product is adequately described, qualitatively and quantitatively.

Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

The manufacturing process is described in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Adequate validation data pertaining to the commercial manufacturing process are available.

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf life are established. The specification includes the parameters appearance (visual), identification (HPLC, UV diode array), potency assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), chiral purity (HPLC), dissolution (Ph. Eur.) and microbiological examination (Ph.Eur.). The corresponding test procedures are validated according to international guidelines. Batch data show consistent quality of the drug product.

The finished product is packaged in PVC/aluminium foil blisters.

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Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. Based on these data, a shelf life of 48 months was established for the dosage strengths 12.5 mg, 25 mg, 50 mg and 100 mg and a shelf life of 36 months for the dosage strengths 150 mg and 200 mg of the finished product. The storage recommendation is “Do not store above 30°C”.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Ontozry (cenobamate), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the assessment reports from the EMA/CHMP (dated 28 January 2021) and US FDA (dated 21 November 2019). The recently finalised rat embryo-fetal development study (post-authorisation commitment with FDA and EMA) was additionally considered.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Ontozry (cenobamate) in the proposed indication. The pharmaco-toxicological profile was sufficiently characterised. Doses tested in the nonclinical studies were limited because of adverse CNS effects, resulting in plasma exposures in the range of or below those at maximum recommended human dose. Adverse effects observed in the general toxicity studies are monitorable and no genotoxic or carcinogenic potential has been detected. A potential for adverse effects was identified in rat and rabbit developmental studies, which is adequately addressed in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The clinical pharmacology data of cenobamate are summarised in the attached information for healthcare professionals; see Appendix of this report. None of the cenobamate clinical pharmacology features is prohibitive for an approval.

6.2 Clinical Aspects

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA.

The available EMA assessment reports and the respective product information for Ontozry (Procedure No. EMEA/H/C/005377/0000) were used as a basis for the clinical evaluation.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ontozry was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Ontozry

Tablets, film-coated tablets

Composition

Active substances

Cenobamate

Excipients

Tablet core

Lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460), silica colloidal (E551), sodium starch glycolate (type A)

Film-coating

25 mg and 100 mg film-coated tablets:

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

50 mg film-coated tablets:

Iron oxide yellow (E172), macrogol, 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, poly(vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171)

Each 12.5 mg tablet contains 39.7 mg lactose monohydrate and 0.16 mg sodium.
Each 25 mg film-coated tablet contains 79.3 mg lactose monohydrate and 0.32 mg sodium.
Each 50 mg film-coated tablet contains 158.7 mg lactose monohydrate and 0.64 mg sodium.
Each 100 mg film-coated tablet contains 108.7 mg lactose monohydrate and 0.64 mg sodium.
Each 150 mg film-coated tablet contains 163 mg lactose monohydrate and 0.96 mg sodium.
Each 200 mg film-coated tablet contains 217.4 mg lactose monohydrate and 1.28 mg sodium.

Pharmaceutical form and active substance quantity per unit

Ontozry 12,5 mg tablets

Each tablet contains 12.5 mg cenobamate.

Uncoated, round, white to off-white tablet with the lettering AV on one side and ‘12’ on the other side.

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

Ontozry 25 mg film-coated tablets

Each film-coated tablet contains 25 mg cenobamate.

Round, brown film-coated tablet with the lettering AV on one side and ‘25’ on the other side.

Ontozry 50 mg film-coated tablets

Each film-coated tablet contains 50 mg cenobamate.

Round, yellow film-coated tablet with the lettering AV on one side and ‘50’ on the other side.

Ontozry 100 mg film-coated tablets

Each film-coated tablet contains 100 mg cenobamate.

Round, brown film-coated tablet with the lettering AV on one side and ‘100’ on the other side.

Ontozry 150 mg film-coated tablets

Each film-coated tablet contains 150 mg cenobamate.

Light orange, round film-coated tablet with the lettering AV on one side and ‘150’ on the other side.

Ontozry 200 mg film-coated tablets

Each film-coated tablet contains 200 mg cenobamate.

Light orange, oval film-coated tablet with the lettering AV on one side and ‘200’ on the other side.

Indications/Uses

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

Dosage/Administration

Usual dosage

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 «Undesirable effects»).

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.

Patients with hepatic disorders

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.

Patients with renal disorders

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.

Elderly patients

The number of patients over the age of 65 in clinical trials of cenobamate was not sufficiently, 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 «Warnings and precautions»).

Children and adolescents

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

Mode 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 «Pharmacokinetics»). 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section «Composition».
Familial Short-QT syndrome (see section «Warnings and precautions»).

Warnings and precautions

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 syndrome with eosinophilia and systemic symptoms (Drug Rash 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 «Undesirable effects»). 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 «Pharmacokinetics»). 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 «Contraindications»).

Excipient of particular interest

Lactose: Patients with rare hereditary problems such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Sodium: This medicine contains less than 1 mmol of sodium (23 mg) per tablet/film-coated tablet, i.e. it is almost "sodium-free".

Interactions

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.

Pharmacokinetic interactions

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.

The following table shows the interactions between cenobamate and other medicinal products.

Table 2: Interactions between cenobamate and other medicinal products and recommendations on concomitant use

Active substance (dosage regimen)	Effect on PK parameters (possible interaction mechanism)	Recommendation on concomitant use
Phenytoin (300 mg/day) Cenobamate (200 mg/day)	Phenytoin: C_{max} +67% (GMR 167% - 90CI 155;180) AUC +84% (GMR 184% - 90CI 169;201) Cenobamate: C_{max} -27% (GMR 73% - 90 CI 69;78) AUC -28% (GMR 72% - 90CI 67;76)	No dose adjustment of cenobamate. Monitoring phenytoin concentrations during cenobamate titration and consider phenytoin dose reduction.
Phenobarbital (90 mg/day) Cenobamate (200 mg/day)	Phenobarbital: C_{max} +34% (GMR 134% - 90CI 128;139) AUC +37% (GMR 137% - 90CI 133;142) Cenobamate: C_{max} -10% (GMR 90% - 90CI 83;99) AUC -15% (GMR 85% - 90CI 77;92)	No dose adjustment of cenobamate. Monitoring phenobarbital concentrations during cenobamate titration and consider phenobarbital dose reduction.
Clobazam (100-400 mg/day) Cenobamate (100-400 mg/day)	Clobazam: possible increase of the active metabolite N-desmethylclobazam Cenobamate: AUC +24% (GMR 124% - 90CI 115;134) (induction of CYP3A4 and inhibition of CYP2C19)	No dose adjustment of cenobamate. Consider clobazam dose reduction.
Lamotrigine Cenobamate (100, 200, and 400 mg/day)	Lamotrigine: dose-dependent decreases in concentrations. Simulated percent change from baseline of -21% (95CI -28;-16), -35% (95CI -43;-27), and -52% (95CI -60;-43) for cenobamate 100, 200, and 400 mg/day) Cenobamate: no significant changes	No dose adjustment of cenobamate. Consider lamotrigine dose increase.
Carbamazepine (400 mg/day) Cenobamate (200 mg/day)	Carbamazepine: C_{max} -23% (GMR 77% - 90CI 71;83) AUC -24% (GMR 76% - 90CI 71;82) Cenobamate: C_{max} -3% (GMR 97% - 90CI 94;101) AUC -3% (GMR 97% - 90CI 95;100)	No dose adjustment required for cenobamate, nor for carbamazepine, as no clinically meaningful decreases in efficacy were observed in patients taking concomitant carbamazepine.
Valproic acid (1000 mg/day) Cenobamate (150 mg/day)	Valproic acid: C_{max} +5% (GMR 105% - 90CI 94;117) AUC +10% (GMR 110% - 90CI 99;121) Cenobamate: C_{max} 0% (GMR 100% - 90CI 98;103) AUC +9% (GMR 109% - 90CI 106;112)	No dose adjustment required.

Active substance (dosage regimen)	**Effect on PK parameters (possible interaction mechanism)**	**Recommendation on concomitant use**
Levetiracetam Cenobamate	Levetiracetam: no significant changes Cenobamate: no significant changes	No dose adjustment required.
Oxcarbazepine Cenobamate	Oxcarbazepine: no significant changes Cenobamate: no significant changes	No dose adjustment required.
Oral contraceptives Cenobamate	Oral contraceptives: reduced exposure of CYP3A4 metabolized contraceptives due to cenobamate induction Cenobamate: no significant changes	Practice additional or alternative non-hormonal measures of birth control.
CYP3A4 substrates (midazolam 2 mg) Cenobamate (100-200 mg/day)	Midazolam: AUC -27% (GMR 73% - 90CI 65;82) and C_{max} -27% (GMR 73% - 90CI 65;83) with cenobamate 100 mg AUC -72% (GMR 28% - 90CI 24;32) and C_{max} -61% (GMR 39% - 90CI 33;45) with cenobamate 200 mg	Consider CYP3A4 substrates dose increase.
CYP2B6 substrates (bupropion 150 mg) Cenobamate (200 mg/day)	Bupropion: C_{max} -23% (GMR 77% - 90CI 67;89) AUC -39% (GMR 61% - 90CI 52;72)	Consider CYP2B6 substrates dose increase.
CYP2C19 substrates (omeprazole 20 mg) Cenobamate (200 mg/day)	Omeprazole: C_{max} +83% (GMR 183% - 90CI 126;267) AUC +107% (GMR 207% - 90CI 144;299)	Consider CYP2C19 substrates dose reduction.
CYP2C9 substrates (warfarin 5 mg) Cenobamate (200 mg/day)	S-Warfarin: C_{max} +7% (GMR 107% - 90CI 96;119) AUC +14% (GMR 114% - 90CI 110;118)	No dose adjustment of CYP2C9 substrates required.
OAT3 substrates (baricitinib, cefaclor, empagliflozin, penicillin G, ritobegron, sitagliptin) Cenobamate	In vitro study (OAT3 inhibition)	Consider OAT3 substrates dose reduction.

GMR = Geometric Mean Ratio; 90CI or 95CI = 90% or 95% Confidence Intervals

Co-administration of inhibitors or inducers should be addressed taking into account references and information as included into the product information of the respective substrate.

Pregnancy, lactation

Women of childbearing potential and contraception in females

Women of childbearing potential must use effective contraception during use of cenobamate and until 4 weeks after treatment discontinuation (see section «Interactions»). Women of reproductive potential concomitantly using oral contraceptives should practice effective additional or alternative non-hormonal measures of birth control during treatment with cenobamate and until 4 weeks after treatment discontinuation (see section «Interactions»).

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 cenobamate 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 «Preclinical data»). Ontozry should not be used during pregnancy unless the clinical condition of the woman requires treatment with cenobamate.

Lactation

It is unknown whether cenobamate or its metabolites are excreted in human milk.
Transfer to milk has been shown in animal studies (see section «Preclinical data»). A risk to the suckling child cannot be excluded. A decision must be made as to whether breastfeeding should be interrupted or whether treatment with cenobamate should be discontinued. Both the benefit of breastfeeding for the child and the benefit of therapy for the woman must be considered.

Fertility

The effects of cenobamate on human fertility are unknown. No sufficient animal data are available due to exposure below clinical levels (see section «Preclinical data»).

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 «Interactions»).

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were somnolence, dizziness, fatigue. visual disturbances, headache and other CNS-related symptoms.

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 undesirable effects
Undesirable effects reported in clinical studies are listed in table 3 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, < 1/10); uncommon (≥ 1/1,000, < 1/100) and rare (≥ 1/10,000, < 1/1,000).

Table 3 Tabulated list of undesirable effects

System organ class	Frequency	Undesirable effectsfrom clinical trials
Immune system disorders	Uncommon	Hypersensitivity*
Psychiatric disorders	Common	Confusional state, Irritability
Nervous system disorders	Very common	Somnolence*38.9%, Coordination and Gait abnormalities*33.0%, Headache 11.3%

	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 specific adverse reactions and additional information

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 «Dosage/Administration» and «Warnings and precautions»).

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 one 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.

Specific populations

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 «Dosage/Administration»).

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Symptoms of overdose are expected to be consistent with the known adverse reactions of Ontozry - somnolence, fatigue and 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.

Properties/Effects

ATC code

N03AX25

Pharmacotherapeutic group: antiepileptics, other antiepileptics

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.

Pharmacodynamics

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 «Warnings and precautions»).

Clinical efficacy

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 4.

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 4 shows the proportion of patients who exhibited a 50% or greater reduction in seizure frequency from baseline.

Table 4: Proportion of patients exhibiting 50% or greater response in Study C017

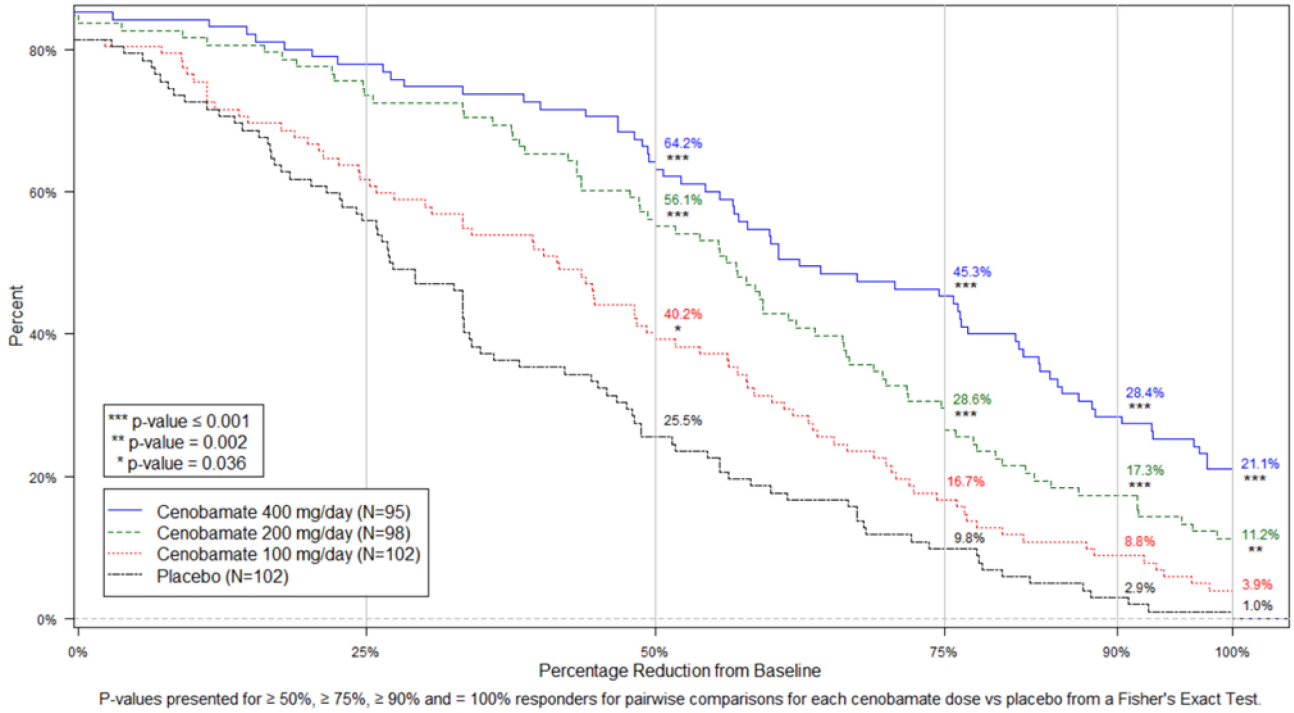
Study	**Standard of care and placebo**	**Standard of care and cenobamate**		
		100 mg/day	200 mg/day	400 mg/day

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 data

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.

Paediatrics

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 «Dosage/Administration»).

Pharmacokinetics

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.

Metabolism

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 (88 % of the dose). 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, while the AUC increased disproportionately in this dose range Steady-state exposures of cenobamate (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.

Kinetics in specific patient groups

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 administration of cenobamate compared to matched healthy controls (see section «Dosage/Administration»). The effect of severe hepatic impairment on cenobamate pharmacokinetics has not been studied.

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 aministration 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 administration of cenobamate (see section «Dosage/Administration»). The effect of haemodialysis on cenobamate pharmacokinetics has not been studied.

Elderly patients

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.

Children and adolescents

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

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.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, 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 adverse CNS effects of cenobamate (including hypoactivity, uncoordinated gait, hypothermia, and tremor). Systemic exposures at NOAEL (no observed adverse effect levels) below exposures reached in humans at the MRHD.

Reproductive toxicity

Reproductive toxicity studies showed adverse effects on embryo-foetal and postnatal development. No adverse effects were observed on fertility. However, systemic exposures at the respective NOAELs for the fertility, embryo-foetal development and pre- postnatal development were bellow human exposure at the MRHD.

Administration of cenobamate to pregnant rats and rabbits during the period of organogenesis resulted in increased embryo-foetal mortality, at dose levels associated with maternal toxicity. In rats, there was a small increase in visceral malformations; however full interpretation of the teratogenic potential at the high dose was not possible due to the high maternal toxicity.

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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Keep out of the reach of children.
Do not store above 30°C.

Instructions for handling

Cenobamate is very persistent in aquatic systems. Any unused medicinal product or waste material should be disposed properly.

Authorisation number

68051 (Swissmedic)

Packs

PVC/aluminium blisters

Ontozry Starter pack 12.5 mg and 25 mg
Pack of 14 tablets of 12.5 mg and 14 film-coated tablets of 25 mg [B]

Ontozry 50 mg
Packs of 14 or 28 film-coated tablets [B]

Ontozry 100 mg
Packs of 14 or 28 film-coated tablets [B]

Ontozry 150 mg
Packs of 14 or 28 film-coated tablets [B]

Ontozry 200 mg
Packs of 14 or 28 film-coated tablets [B]

Not all pack sizes may be marketed.

Marketing authorisation holder

Arvelle Therapeutics International GmbH, Zug

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May 2022