ONTOZRY®: a guide for healthcare professionals

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events and product complaints should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard for the UK or www.hpra.ie for Ireland. Adverse events and product complaints should also be reported to Angelini Pharma on (UK) +44 2034889643, (ROI) +353 1 584 4671 or UKIReporting@angelinipharma.com

Indication for United Kingdom: ONTOZRY® is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.[1]

Indication for Republic of Ireland: 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.[1]

Prescribing information and adverse event reporting information can be found by scanning the QR code or **click here** if you are viewing on a digital device.

Angelini Pharma

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Contents

Contact an Angelini Epilepsy Account Specialist

If you have further questions about ONTOZRY® or on supporting patients taking ONTOZRY®, **please contact your local Angelini Epilepsy Account Specialist**

My Angelini Epilepsy Account Specialist: _____

Telephone: _____

Email: _____

How to use this guide

This guide has been developed to help you support your patients with epilepsy whose focal-onset seizures are drug resistant, and have been prescribed ONTOZRY®.

This guide provides you with clinical information on ONTOZRY® (cenobamate), as well as support on in-clinic use.

People with drug-resistant epilepsy may be feeling fatigued, anxious and depressed because of their condition and its impact on daily living.[2] This guide can support you in providing patients with the information they need and reassuring them about their treatment plan.

This guide has 3 sections:

SECTION 1 **'About ONTOZRY®' contains:**

- Therapeutic indication
- Dual complementary mechanism of action
- Efficacy and tolerability data reported in ONTOZRY® clinical trials

SECTION 2 **'Prescribing ONTOZRY® in adults' is a specific section for prescribers:**

- Determining which of your patients may be suitable for ONTOZRY®
- Important prescribing considerations
- Information on guiding titration to achieve the maintenance dose

SECTION 3 **'Supporting your patients throughout treatment' suggests how and when to offer patients support throughout their treatment:**

- How to support and empower patients in the management of their condition
- Support with helping your patients communicate more effectively

Who can use this guide?

This guide was developed for all healthcare professionals (HCPs) who are involved in caring for patients with drug-resistant focal epilepsy. The 'Prescribing ONTOZRY® in adults' section is of particular relevance to HCPs involved in the pharmacotherapeutic management of patients.

SECTION 1

About ONTOZRY®

Therapeutic indication[1]

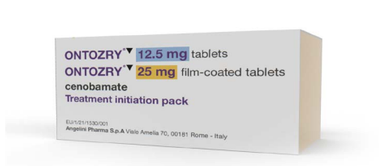
Indication for United Kingdom: ONTOZRY® is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.[1]

Indication for Republic of Ireland: 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.[1]

ONTOZRY® is available in initiation, titration and maintenance packs

Designed to support patients at each stage of their treatment journey.

Initiation pack
(28 days)

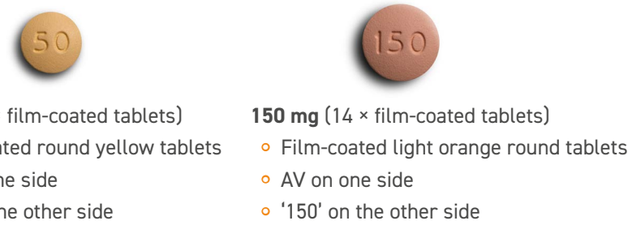


Not actual size

12.5 mg (14 × tablets)
- Uncoated round white to off-white tablets
- AV on one side
- '12' on the other side

25 mg (14 × film-coated tablets)
- Film-coated round brown tablets
- AV on one side
- '25' on the other side

Titration pack
(to be used until optimal dose is reached)



50 mg (14 × film-coated tablets)
- Film-coated round yellow tablets
- AV on one side
- '50' on the other side

150 mg (14 × film-coated tablets)
- Film-coated light orange round tablets
- AV on one side
- '150' on the other side

100 mg (14 × film-coated tablets)
- Film-coated round brown tablets
- AV on one side
- '100' on the other side

200 mg (14 × film-coated tablets)
- Film-coated oval, light orange tablets
- AV on one side
- '200' on the other side

Maintenance pack
(optimal dosing)

Available packs:

50 mg
- 28 × film-coated tablets
- 84 × film-coated tablets

150 mg
- 28 × film-coated tablets
- 84 × film-coated tablets

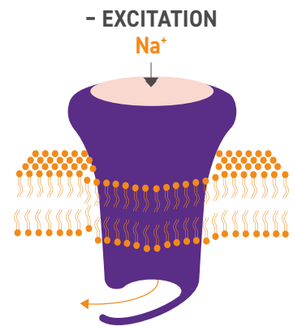
100 mg
- 28 × film-coated tablets
- 84 × film-coated tablets

200 mg
- 28 × film-coated tablets
- 84 × film-coated tablets

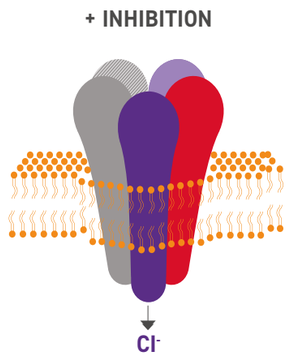
Product images for illustration purposes only

Dual complementary mechanism of action (MoA)[1]

ONTOZRY® is a small molecule anti-seizure medication (ATC code: N03AX25). While the precise MoA is unknown, it is thought to elicit a dual MoA:[1]



1) Reduces repetitive neuronal firing by enhancing the inactivation of sodium channels and by preferentially inhibiting the persistent component of the sodium current[1]



2) Increases gamma-aminobutyric acid ($GABA_A$) receptor response

While the precise MoA is unknown, the dual MoA of cenobamate suggests that it has the potential to **both prevent seizure initiation and limit seizure spread.**[3-7]

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.

ONTOZRY® in the treatment pathway

ONTOZRY® is an option for your patients whose focal-onset seizures are uncontrolled despite treatment with at least 2 anti-epileptic medicinal products.[1]

First anti-epileptic medicinal product → **Second anti-epileptic medicinal product (monotherapy or dual)** → **Add ONTOZRY® to second-line treatment**

FACT **Drug resistance** (failure to control seizures after 2 different anti-seizure medications) affects **~40%** of patients.[8-10]

FACT **Drug resistance reduces probability of treatment success**

With every unsuccessful anti-seizure medication, the probability of patients achieving seizure freedom* diminishes significantly.[9,10] ONTOZRY® may be a treatment option for these patients.

National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) Guidance on ONTOZRY®

NICE recommends ONTOZRY® as an option for treating focal-onset seizures with or without secondary generalised seizures in adults with drug-resistant epilepsy that has not been adequately controlled with at least 2 anti-seizure medicines.[11] ONTOZRY® is recommended only as a second-line add-on treatment if:[11]

- it is used after at least 1 first-line add-on treatment has not controlled seizures, and other first-line add-on treatments are contraindicated or not tolerated, and
- treatment is started by a healthcare professional with expertise in epilepsy, after which treatment can be continued in primary care.

This recommendation is not intended to affect treatment with cenobamate that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.[11]

For more information, refer to the full NICE guidance.[11]

SMC have also accepted ONTOZRY® for restricted use in Scotland for patients with drug-resistant epilepsy as a second-line adjunctive anti-seizure medicine, after the failure of the first adjunctive anti-seizure medicine.[12]

In patients with uncontrolled focal seizures, despite treatment with anti-epileptic medicines, cenobamate was superior to placebo in terms of the proportion of patients experiencing a ⩾50% reduction in focal seizure frequency.[12]

Administration of ONTOZRY®

ONTOZRY® offers once-daily (OD) oral dosing at any time.

The terminal half-life is 50–60 hours within the therapeutic range of 100 to 400 mg OD.[1]

Starting dose

To be **titrated gradually** to a target maintenance dose of 200 mg (based on clinical response, dose may be increased to a maximum of 400 mg per day by increments of 50 mg per day every 2 weeks)[1]

Missed doses

If a patient misses one dose, they should take a single dose as soon as they remember, unless it is **less than 12 hours until their next regularly scheduled dose**[1]

Oral route of administration

To be taken with a **glass of water**, **with or without food**, preferably at the **same time** each day[1]
The tablet can also be crushed, then mixed with water and administered orally or via a nasogastric tube[1]

* Defined as being free of seizures for ⩾12 months.

ONTOZRY® clinical trial programme

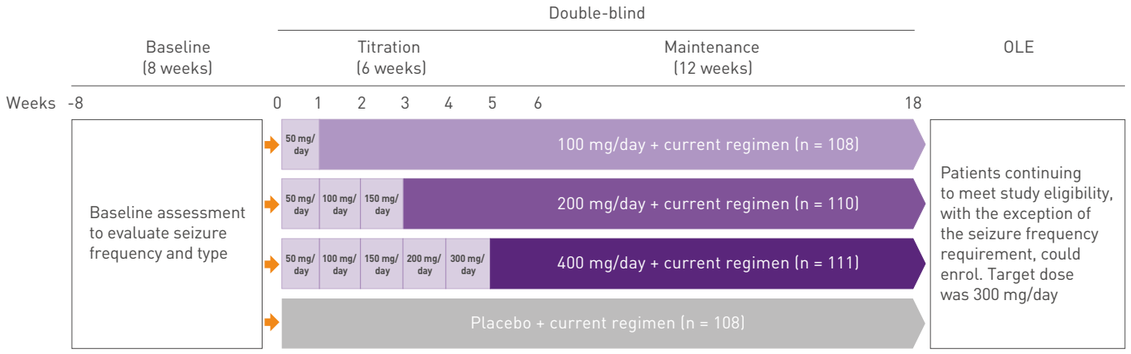
The clinical trial programme of ONTOZRY® is based on three key trials (studies 013, 017 and 021) involving over 1,900 patients with uncontrolled focal-onset seizures. Details of Study 021 can be found on page 15.

Study 017:[13,14] Pivotal trial	Study 013[15,16]
A multicentre, double-blind, randomised, adjunctive placebo-controlled trial to evaluate the efficacy and safety profile of ONTOZRY® in patients with treatment-resistant focal-onset seizures	A multicentre, double-blind, randomised, adjunctive placebo-controlled trial to evaluate the efficacy and safety profile of ONTOZRY® in patients with treatment-resistant focal-onset seizures
Baseline (8 weeks)* ONTOZRY® titration (double-blind; 6 weeks): ◦ 50 mg OD × 1 week, followed by weekly increments until reaching the target doses of 100 mg, 200 mg and 400 mg OD Maintenance (double-blind; 12 weeks) ◦ 100 mg, 200 mg or 400 mg OD Open label extension (OLE): 300 mg	Baseline (8 weeks)* ONTOZRY® titration (double-blind; 6 weeks): ◦ 50 mg OD × 2 weeks ◦ 100 mg OD × 2 weeks ◦ 150 mg OD × 2 weeks Maintenance (double-blind; 6 weeks) ◦ 200 mg OD OLE: 100–400 mg
N = 437 OLE N = 355	N = 222 OLE N = 149
Primary endpoints: ◦ Responder rate defined as a 50% or greater reduction in seizure frequency during maintenance phase	Primary endpoint: ◦ Percentage change from baseline in seizure frequency during double-blind period
Secondary endpoints: ◦ 100% responder rates ◦ Seizure frequency by seizure type	Secondary endpoints: ◦ Responder rate defined as a 50% or greater reduction in seizure frequency ◦ Seizure frequency by seizure type

* The titration schedule in the C017 and C013 studies started at higher doses (50 mg or 100 mg once daily) and titrated rapidly (weekly or faster titration). Owing to the potential for serious adverse reactions, the recommended titration schedule should not be exceeded. 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.

Clinical trials

Study 017 Phase III trial: Krauss GL *et al.*, 2020[13]



Primary endpoint
- ⩾50% reduction in seizure frequency from baseline during 12-week maintenance phase

Key secondary endpoints
- ⩾75%, ⩾90% and 100% reduction in seizure frequency
- Change in seizure frequency by seizure type

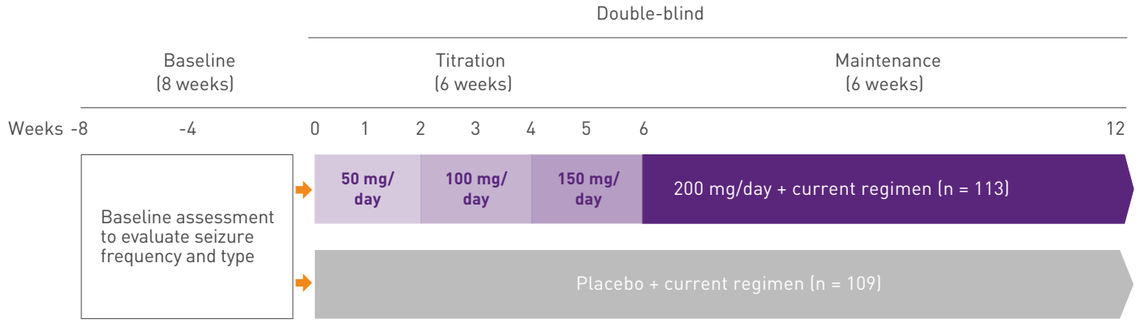
The primary endpoint was responder rate, defined as the percentage of patients achieving ⩾50% reduction from baseline in focal seizure frequency during the 12-week maintenance phase, and the results of this are presented.

Selected secondary endpoints included:
- the percentage change in seizure frequency during the 12-week maintenance phase
- the responder rate for patients during the 18-week double-blind treatment period
- responder rates for 75% or more, 90% or more, and 100% reduction in seizures
- percentage change from baseline in seizure frequency per 28 days by seizure type (focal-aware with motor component, focal with impaired awareness, or focal to bilateral tonic-clonic seizures)

Open-label extension

At completion of the double-blind period, patients who continued to meet study eligibility, with the exception of the seizure frequency requirement, could enrol in an OLE. Participants underwent a blinded 2-week conversion to a target dose of ONTOZRY® 300 mg/day.[13,14]

Study 013 Phase II trial: Chung SS *et al.*, 2020[15]



Primary endpoint
- Percentage change from baseline in focal seizure frequency per 28 days during the double-blind treatment period (both titration and maintenance phases)

Key secondary endpoints
- Responder rate (⩾50% reduction in seizure frequency)
- Assessment of seizure frequency by seizure type

The primary endpoint was the percentage change from baseline in focal seizure frequency per 28 days during the double-blind treatment period (both titration and maintenance phases).

Selected secondary endpoints included:
- responder rate, defined as a ⩾50% reduction in seizure frequency
- assessment of seizure frequency by seizure type (focal aware with motor component, focal with impaired awareness, or focal to bilateral tonic-clonic seizures)

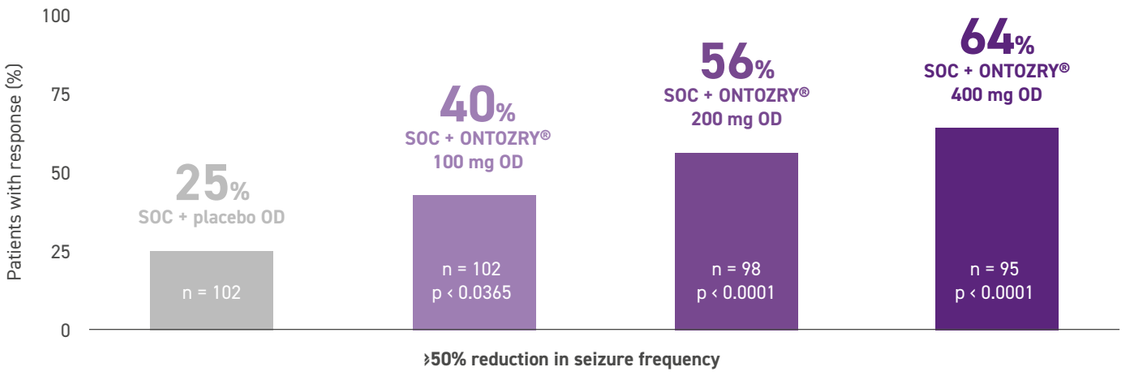
Safety outcomes were also assessed (incidence of treatment-emergent adverse events, serious adverse events, treatment discontinuations). Any patient reporting a rash was evaluated for drug hypersensitivity.

Clinical efficacy

Study 017 primary endpoint: Standard of care (SOC) + ONTOZRY® reduced seizure frequency by at least 50% compared with SOC + placebo[13]

Compared with 25% of patients in the SOC + placebo treatment arm:

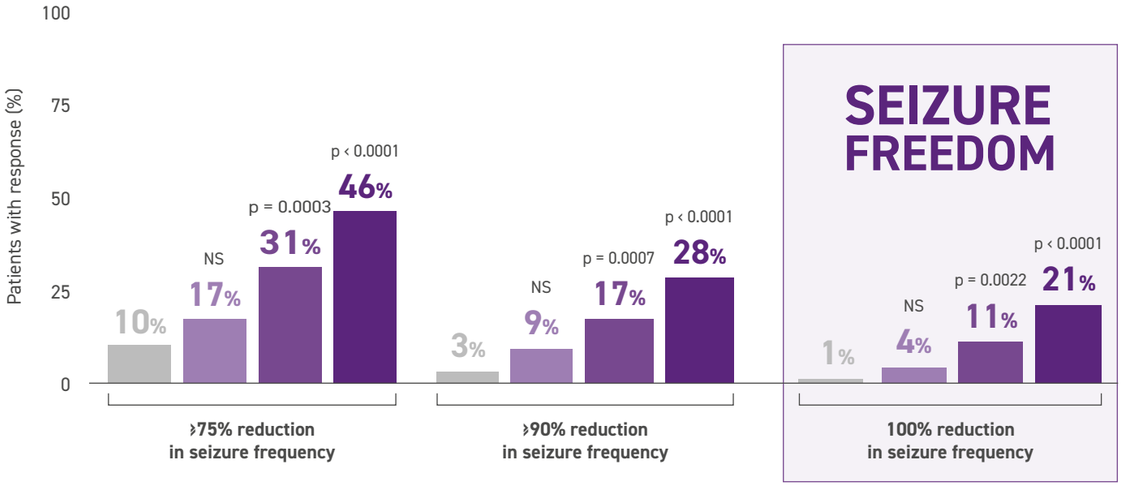
- 56% of patients experienced at least 50% reduction in seizure frequency per 28 days with SOC + ONTOZRY® 200 mg
- 64% of patients experienced at least 50% reduction in seizure frequency per 28 days with SOC + ONTOZRY® 400 mg



SOC, standard of care: treatment with up to 3 concomitant anti-seizure medications.
Patients in the ONTOZRY® arm were titrated over 6 weeks and received maintenance dosing for 12 weeks.
Modified intention-to-treat maintenance phase population in patients with uncontrolled focal-onset seizures.
Adapted from Krauss GL, *et al.*, 2020.[13]

Study 017 secondary endpoint: 100% reduction in seizure frequency was significantly higher with SOC + ONTOZRY® vs SOC + placebo[13]

Seizure freedom (100% reduction) over a 12-week period was experienced by 11% and 21% of patients treated with SOC + ONTOZRY® 200 mg and 400 mg respectively – significantly higher than the 1% treated with SOC + placebo; p < 0.01



SOC, standard of care: treatment with up to 3 concomitant anti-seizure medications. NS, not significant.
Patients in the ONTOZRY® arm were titrated over 6 weeks and received maintenance dosing for 12 weeks.
Modified intention-to-treat maintenance phase population in patients with uncontrolled focal-onset seizures.
Adapted from Krauss GL, *et al.*, 2020.[13]

SOC + placebo OD (n = 102)
SOC + ONTOZRY® 100 mg OD (n = 102)
SOC + ONTOZRY® 200 mg OD (n = 98)
SOC+ ONTOZRY® 400 mg OD (n = 95)

Similar responses were seen across **subpopulations** regardless of baseline seizure frequency or disease duration.[1]

Study 017 secondary endpoint: SOC + ONTOZRY® significantly reduced seizure severity vs SOC + placebo[13]

Reduction in seizure severity was defined as a decrease in seizure frequency across different types of focal-onset seizures, including more severe focal to bilateral tonic-clonic seizures:

- Focal to bilateral tonic-clonic 28-day seizure frequency was reduced by up to 92% with SOC + ONTOZRY® 200 mg/400 mg vs 33% in SOC + placebo
- 28-day frequency of multiple types of focal-onset seizures was significantly reduced with SOC + ONTOZRY® 200 mg and 400 mg vs SOC + placebo; p < 0.001 for all

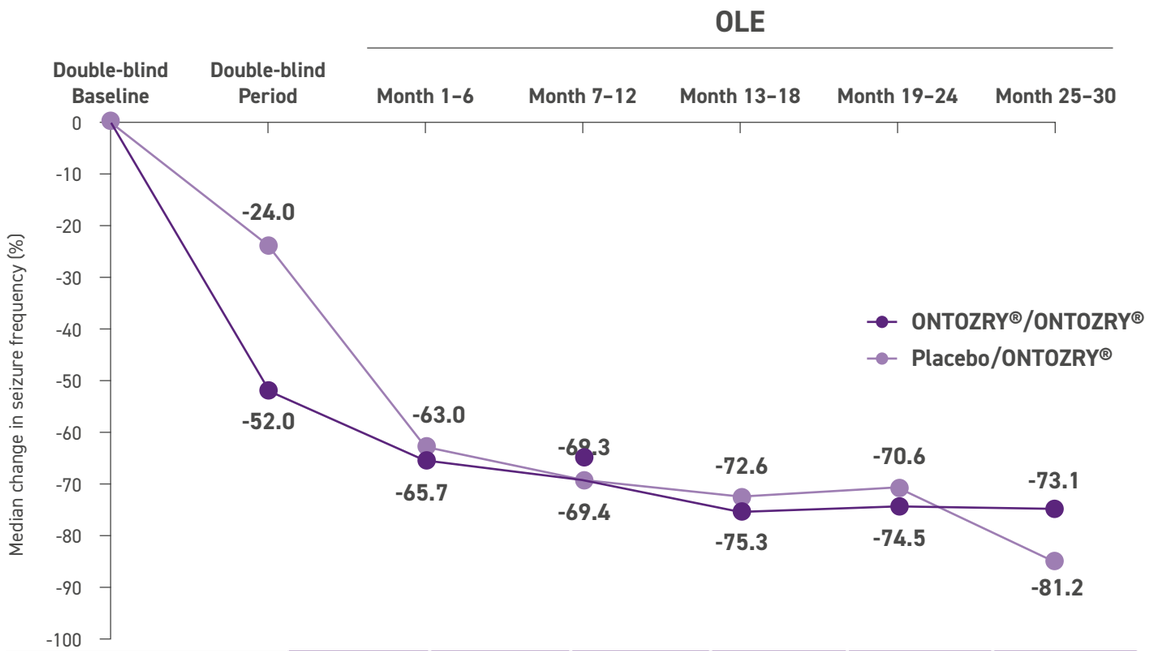
SEIZURE TYPE	SOC + placebo OD	SOC + ONTOZRY® 200 mg OD	SOC + ONTOZRY® 400 mg OD
Focal aware seizures	11.0% (n = 17)	-62.0% (n = 24, p = 0.001)	-69.0% (n = 20, p = 0.0001)
Focal-onset seizures	-29.0% (n = 87)	-55.0% (n = 87, p = 0.0003)	-61.5% (n = 86, p < 0.0001)
Focal to bilateral tonic-clonic seizures	-33.0% (n = 43)	-92.0% (n = 32, p = 0.0003)	-83.0% (n = 36, p = 0.0045)

SOC, standard of care: treatment with up to 3 concomitant anti-seizure medications.
Adapted from Krauss GL *et al.*, 2020.[13]

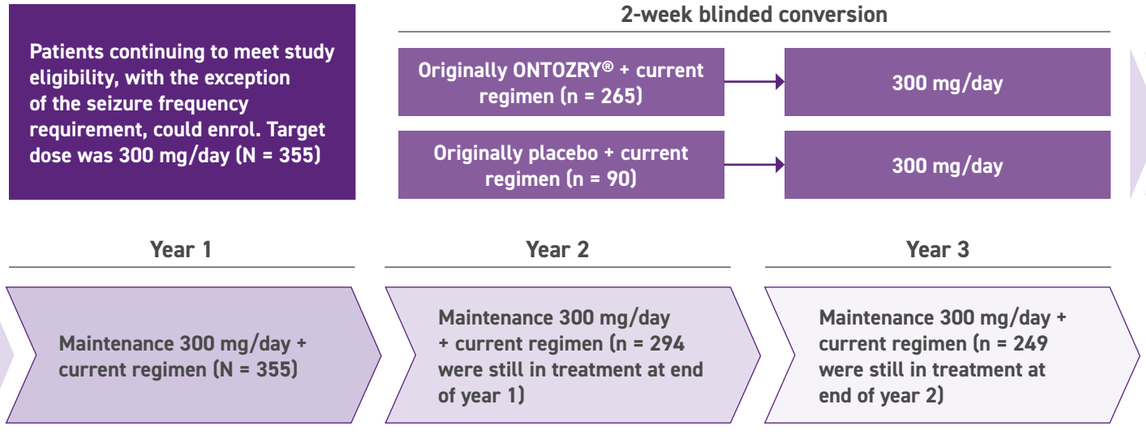
- 53% of patients with focal to bilateral tonic-clonic seizures were free from these seizures over a 12-week period when taking SOC + ONTOZRY® 400 mg vs 26% in SOC + placebo

Reductions in seizure frequency were maintained up to 30 months with SOC + ONTOZRY®[14]

Long-term treatment with ONTOZRY® (up to 30 months) reduced the frequency of seizures – an effect that was seen from month 1 to 6 of OLE treatment in patients initially treated with placebo during the double-blind phase of study 017 and patients who received ONTOZRY® throughout. All data presented are those provided in the paper.



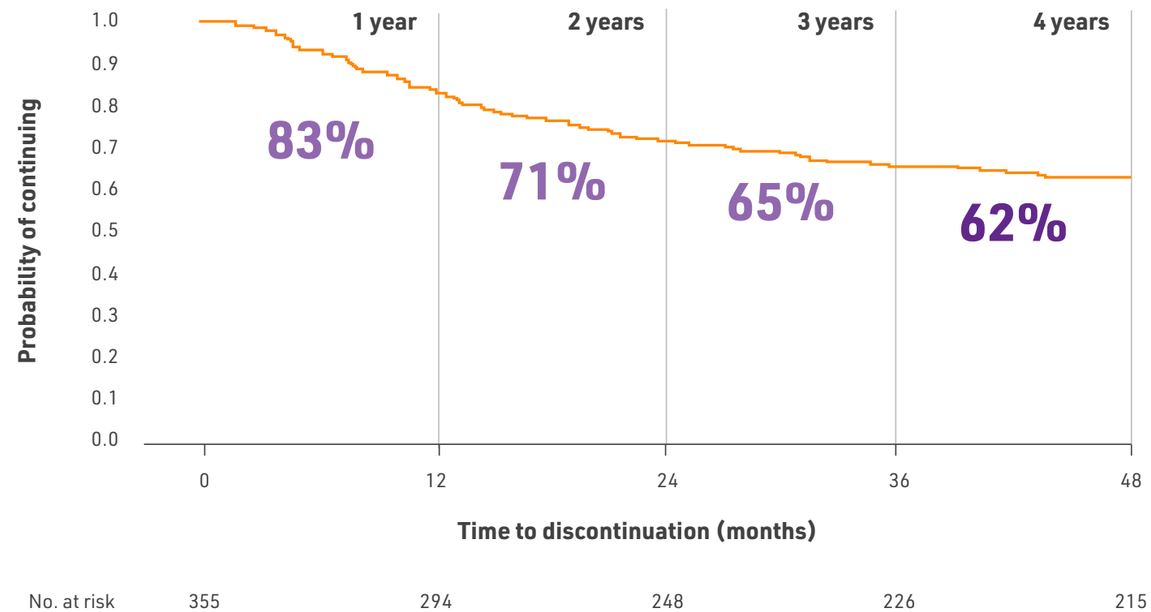
Group, n	Double-blind phase	Month 1–6	Month 7–12	Month 13–18	Month 19–24	Month 25–30
ONTOZRY®/ONTOZRY®	328	264	232	202	185	175
Placebo/ONTOZRY®	106	90	80	70	64	62



Patients entering the OLE underwent a 2-week blinded conversion to a target dose of ONTOZRY® 300 mg OD.
During the 2-week conversion, the investigator could increase or decrease the open-label dosage, if clinically indicated, to a minimum of 50 mg and maximum of 400 mg/day.

Long-term retention rates during OLE study

The majority of patients (99%) opted to enter the OLE of study 017, with **62%** of patients remaining in the study for at least 48 months with treatment at **2 years.**[14]



Safety profile and tolerability

Study 021[17]

An open-label, multicentre safety and pharmacokinetic study of ONTOZRY® as adjunctive therapy in subjects with focal-onset seizures

Designed to characterise the rate of drug reaction with eosinophilia and systemic symptoms (DRESS)

ONTOZRY® titration (12 weeks):
- 12.5 mg OD × 2 weeks
- 25 mg OD × 2 weeks
- 50 mg OD × 2 weeks: thereafter 50 mg OD increments at 2-week intervals until target dose of 200 mg OD

Maintenance (12+ months)
- Max dose 400 mg OD

N = 1,339
n exposed to ONTOZRY® for ⩾6 months = 1,100
n exposed to ONTOZRY® for ⩾12 months = 306

Primary endpoints:
- Safety assessment
- Effect of cenobamate on pharmacokinetics of phenytoin and phenobarbital

Safety profile and tolerability

Most treatment-emergent adverse events with ONTOZRY® were mild or moderate[13,15,17] and dose-dependent[13]

The most commonly reported adverse reactions were somnolence, dizziness, fatigue and headache in study 017.[1] Please refer to the ONTOZRY® Summary of Product Characteristics for further details.

Adverse reactions reported in pooled clinical studies by system organ class and frequency:[1]

Frequency	System organ class	Adverse reactions from clinical trials
Very common (occurs in ⩾1/10 patients)	Nervous system disorders	Somnolence Coordination and gait abnormalities Headache
Common (occurs in ⩾1/100 to <1/10 patients)	Nervous system disorders	Dysarthria Nystagmus Aphasia Memory impairment
	Psychiatric disorders	Confusional state Irritability
	Eye disorders	Diplopia Vision blurred
	Gastrointestinal disorders	Constipation Diarrhoea Nausea Vomiting Dry mouth
	Skin and subcutaneous tissue disorder	Rash
	Investigations	Hepatic enzyme increased
Uncommon (occurs in ⩾1/1000 to <1/100 patients)	Immune system disorders, Psychiatric disorders	Hypersensitivity, suicidal ideation
Rare (occurs in ⩾1/10000 to <1/1000 patients)	Skin and subcutaneous tissue disorder	DRESS

Selected adverse reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Three cases of DRESS were reported within 2–4 weeks of starting ONTOZRY® in studies with high starting doses (50 mg or 100 mg OD) and weekly or faster titration. Initiating ONTOZRY® at a lower dose and slowing the initial titration rate may lower the rate of DRESS.[17] One case of DRESS was reported in the C021 study;[17] please refer to the SmPC for the recommended titration schedule.

Symptoms of DRESS may include: fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia.

If signs and symptoms suggestive of these reactions appear, **withdraw ONTOZRY® immediately** and consider an alternative treatment.

Advise patients on signs and symptoms of DRESS and monitor them closely for skin reactions.

Hypersensitivity[1]

In clinical trials, two patients treated with ONTOZRY® experienced drug hypersensitivity (one patient had hypersensitivity, and one patient experienced eyelid oedema). One placebo-treated patient experienced hypersensitivity. All events were classified as mild or moderate.

SECTION 2

Prescribing ONTOZRY® in adults

Considerations for prescribers[1]

Below is a quick-reference checklist to determine if a patient is eligible for ONTOZRY®, and clinical dose considerations. Please refer to the ONTOZRY® Summary of Product Characteristics for further details:[1]

Determine eligibility for ONTOZRY®

Indication for United Kingdom: ONTOZRY® is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.[1]

Indication for Republic of Ireland: 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.[1]

Check if the patient belongs to a special population

Elderly (≥65 years)

- 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 a 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

Renal impairment

- ONTOZRY® 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 OD**
- ONTOZRY® should not be used in patients with **end-stage renal disease** or patients undergoing **haemodialysis**

Hepatic impairment

- Exposure to ONTOZRY® 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 OD**
- ONTOZRY® should not be used in patients with severe hepatic impairment

Check for contraindications

- Hypersensitivity to cenobamate or to any of its excipients
- Familial Short-QT syndrome
  - Exercise caution when prescribing ONTOZRY® in combination with other medicinal products that are known to shorten the QT
  - **ONTOZRY® must not be used in patients with Familial Short-QT syndrome** (a rare genetic syndrome associated with an increased risk of sudden death and ventricular arrhythmias)

Note special warning on suicide ideation

- Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products including 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

Check for potential drug–drug interactions

Other anti-seizure medications

When used concomitantly with ONTOZRY®, **no dosage adjustments** are needed for:

- Carbamazepine
- Levetiracetam
- Valproic acid
- Lacosamide
- Oxcarbazepine

Recommended dose adjustments depending on individual patient response:

Concomitant anti-seizure medication	ONTOZRY®
Lamotrigine	Depending on individual response, the dose of ONTOZRY® may need to be increased
Clobazam • May require dose reduction	No dose adjustment required
Phenobarbital • May require dose reduction based on individual response • Phenobarbital concentration should be monitored during ONTOZRY® titration	
Phenytoin • May require dose reduction based on individual response • Phenytoin concentration should be monitored during ONTOZRY® titration	

Other medicinal products

Adding ONTOZRY® may require the following adjustments:

Oral contraceptives	Cenobamate showed a dose-dependent induction of CYP3A4; since hormonal contraceptives may be metabolised by CYP3A4, their efficacy may be reduced by concomitant use with cenobamate. Women of reproductive potential, concomitantly using oral contraceptives, should therefore practise additional or alternative non-hormonal measures of birth control during treatment with ONTOZRY® and until 4 weeks after treatment discontinuation
CYP3A4 substrates (e.g. midazolam)	Dose of medication metabolised by CPY3A4 may be required to be increased
CYP2B6 substrates (e.g. bupropion)	Dose of medication metabolised by CYP2B6 may be required to be increased
CYP2C19 substrates (e.g. omeprazole)	Dose of medication metabolised by CYP2C19 may be required to be reduced

Women of childbearing potential

- 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

Fertility, pregnancy and lactation

- 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
- 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
- It is unknown whether cenobamate or its metabolites are excreted in human milk. As a precautionary measure, breastfeeding should be discontinued during treatment with ONTOZRY®
- The effects of cenobamate on human fertility are unknown. Animal data are insufficient due to exposure below clinical levels

Alcohol

- Use of ONTOZRY® with alcohol may increase the risk of neurological adverse reactions

Explaining the oral administration[1]

ONTOZRY® is taken as a **daily 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.

The tablet should be swallowed whole, with a glass of water. The tablets cannot be split accurately as there is no break line and the accuracy of the dose cannot be ensured.

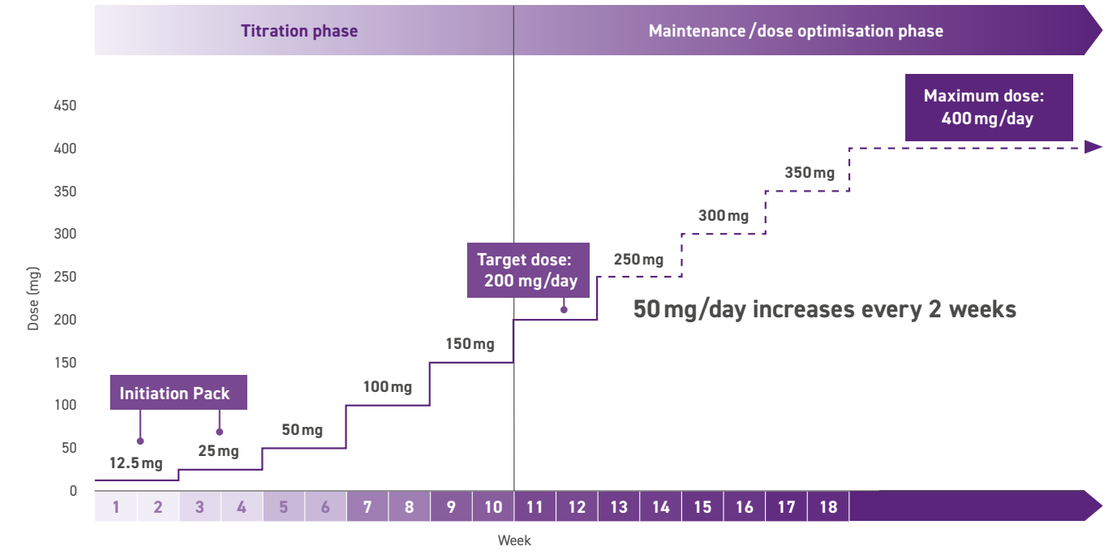
The tablet can also be crushed, then mixed with water and administered orally or via a nasogastric tube.[1]

Selecting the titration regimen[1]

The recommended starting dose of ONTOZRY® is **12.5 mg OD**, titrated gradually (Q2W) to reach the recommended target dose of **200 mg OD**. The dose may be further increased to a maximum of **400 mg OD** based on the individual needs.

Please consider the dosing adjustments specified in the checklist. These include:

- Use in special populations
- Potential drug–drug interactions



Gradual (Q2W*) titration is very important, since exceeding the recommended titration schedule (provided above) may increase the potential for serious adverse reactions.[1]

If required, 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.

Explaining the titration regimen

Below are some pointers that may be useful in this conversation and resources that are available to support them:

ONTOZRY® Patient Support Guide. This important patient resource contains an explanation of the titration period and a '**Titration Plan**', which may be helpful to use with your patient.

Your ONTOZRY® Titration Diary. Encourage patients to use the **Your ONTOZRY® Titration Diary to help keep them on track with their titration**. There is space to include notes on how well they think their treatment is working, and how their condition is affecting daily activities.

Patients have been instructed to ask their nurses should they require extra copies.

* Once every 2 weeks.

Explain to patients:

- Titration is important because it helps to limit possible side effects by taking time to see how your body will react to the medicine
- Everybody is different; we will create a titration plan that is specific for you
- Your **ONTOZRY® Titration Diary** will support you throughout your titration
- Your doctor or nurse will start with the lowest dose and then every couple of weeks, your healthcare team will adjust your dose. In most cases, it will be to 'step-up' (increase) your dose
  - However, you may find sometimes we will need to step down (decrease) your dose. It all depends on your needs, so remember to follow the latest plan
- The titration will take 10 weeks – **or longer**, **depending on your needs**. By the end of the titration period, we will have reached your maintenance dose

In the **Your ONTOZRY® Titration Diary**, use the **Titration Plan** to **mark out the planned doses** for the titration period. Patients will then have a clear idea of what dose to take every two weeks.

Titration week number and daily ONTOZRY® dose				
1 Date: _____ mg	**2** Date: _____ mg	**3** Date: _____ mg	**4** Date: _____ mg	**5** Date: _____ mg
6 Date: _____ mg	**7** Date: _____ mg	**8** Date: _____ mg	**9** Date: _____ mg	**10** Date: _____ mg
Use these extra weeks if you need them				
Date: _____ mg	Date: _____ mg	Date: _____ mg	Date: _____ mg	Date: _____ mg

It is important that you explain to patients:

- Their Titration Plan **may change over time**, for instance, if any step-downs are required during titration
- The recommended titration period is **at least 10 weeks**, but there are extra weeks marked in the diary, should the titration require more time to complete
  - Reassure patients that titration periods beyond 10 weeks does not mean that they are not doing well with their medication; **every patient is different**

Patients may need support managing their titration

Consider organising a brief follow-up call to patients to help keep track of their adherence and proactively address any problems.

Key information about side effects to explain to your patients[1]

Alcohol

- Caution is advised when drinking alcohol when you are taking ONTOZRY®, as it may increase the risk of problems with thinking, judgement and memory

DRESS

- Although rare, DRESS can be life-threatening or fatal
- **Advise patients of the signs and symptoms of DRESS**
- Monitor patients closely for skin reactions
- Symptoms of DRESS typically include: 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, **ONTOZRY® should be withdrawn immediately** and an alternative treatment considered.

Suicidal ideation and behaviour

- Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicinal products including cenobamate
- Patients should be monitored for signs of suicidal ideation and behaviour, 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

QT-shortening

- A dose-dependent shortening of the QTcF interval, has been observed with cenobamate
- Use caution when prescribing cenobamate in combination with other medicinal products that are known to shorten the QT

Lactose

- This drug contains lactose and patients with rare hereditary problems such as galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine

Effect on ability to drive and use machines

- ONTOZRY® has moderate influence on the ability to drive and use machines
- ONTOZRY® may cause **somnolence, dizziness, fatigue, impaired vision and other CNS-related symptoms**, which may influence the ability to drive or use machines
- Advise patients 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

For patients of childbearing potential

- Confirm patient is not pregnant or breastfeeding
- Confirm effective form(s) of contraception in patients of childbearing potential

Refer to **Section 2 – Considerations for prescribers** for further information of ONTOZRY® in pregnancy

Final check: check that your patient:

- Understands your rationale for prescribing ONTOZRY® – because they have not responded to at least 2 anti-seizure medications for their epilepsy
- Understands how ONTOZRY® should be taken and that it must be taken in addition to their existing anti-seizure medication
- Understands the key safety information
- Is able to perform titration
- Knows how to contact the healthcare team if they have any questions or concerns

SECTION 3

Supporting your patients throughout treatment

Patient empowerment comes from **education** and having **confidence in their care plan.**[18] To help patients get the most out of ONTOZRY®, it is important for them to understand the rationale of why they may benefit from ONTOZRY® treatment.

By this point in their treatment journey, patients may be feeling tired, depressed and anxious about their condition,[1] and may seek reassurance that you still have a clear treatment plan for them. Patient vulnerabilities and challenges to consider may include **poor medication adherence** and **cognitive impairments**.

The following sections cover patient factors to consider along with a patient-friendly discussion aid to facilitate clear communication with your patients throughout treatment.

Promoting adherence to medication

Nearly **2** in **5** patients (**39%**) are **non-adherent** to anti-seizure medications[19]

Non-adherence to medication can lead to **loss of seizure control**[20]

Conversely, **well-controlled epilepsy** could lead to non-adherence[21]

For your patients struggling with adhering to medication:

- Acknowledge the challenges of medication adherence on top of busy lifestyles
- Warn that missing doses can increase their risk of having a seizure. Not following the Titration Plan and/or not taking their medication regularly may increase their risk of getting side effects and seizures
- Determine the cause of non-adherence so you can address it:
  - Unintentional: forgetfulness, inability to follow titration, dysphagia
  - Intentional: fears about side effects, dependence, misperceptions, lifestyle choices

Talking to your ONTOZRY® patients
Suggested conversation prompts

Let's build some good habits

- It doesn't matter when in the day you take ONTOZRY® but it is a good idea to decide on a set time to help you remember. Examples are:
  - After brushing your teeth in the morning
  - After breakfast
  - Last thing at night
- Keep your medicine in a convenient place (but out of the reach and sight of children)

There are several ways to help keep you on track with your medicine:

- Set an alarm on your phone
- Use an automatic pill dispenser
- Ask the pharmacy to arrange dosette boxes, so that you know when and what medicines to take

Setting expectations

Setting realistic expectations can keep patients engaged with their treatment and reassure them on what to expect. Ensure patients are clear on particular signs to look out for during treatment, and that they know how to contact the healthcare team if they have any queries or concerns.

Talking to your ONTOZRY® patients
Suggested conversation prompts

What to expect with your treatment

- Just like epilepsy is different for each person, results – and the time taken for you to start feeling them – may also vary. By taking ONTOZRY® as directed, along with your other epilepsy medicine, you may notice improvements in your condition[1]
- Clinical trials of ONTOZRY® have shown that:[13]

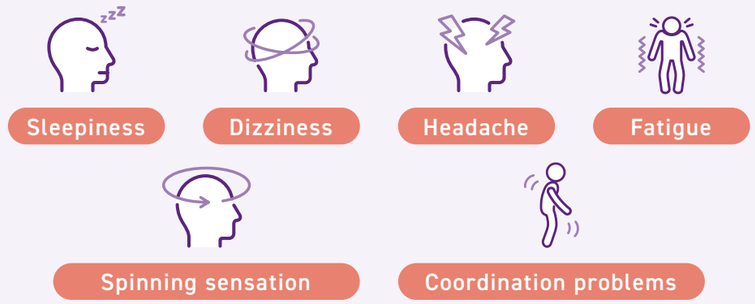
More than **1** in **2** people had their number of seizures reduced by at least half over a 12-week period

Around **1** in **10** people were seizure-free on ONTOZRY® 200 mg over a 12-week period. At the highest ONTOZRY® dose (400 mg), this was doubled

- If you feel that your medicines are not working, speak to us, and we will see how we could help

Reminding patients what they need to look out for[1]

- Not everyone gets side effects from ONTOZRY®, but if you think you are having a side effect, make a note of it in **Your ONTOZRY® Titration Diary** and let us know
  - We will be able to give you advice and manage your side effect, if necessary
  - We will work out if you are having a side effect due to your treatment or if it is a symptom caused by your epilepsy
- These side effects are very common and may affect at least 1 in 10 people:



- Tell us right away if you experience a fever, flu-like symptoms, a rash on your face, a rash spreading to other parts of your body, or swollen glands (enlarged lymph nodes). This is a rare side effect but it's important you stay alert and let us know if you think you have any of these signs

Guidance for adverse event management[1]

- The titration schedule should be strictly followed[1]
- If your patient experiences any symptoms of DRESS, with or without rash, withdraw ONTOZRY® immediately[1]

Adjustments to ONTOZRY®	Adjustments to concomitant anti-seizure medication(s)
In the pivotal phase III trial, people who started titration at a low dose and were titrated slowly did not develop symptoms of DRESS[1]	Lower the dose of concomitant anti-seizure medications (especially benzodiazepines and sodium-channel blockers with sedating properties)[1]

Helping patients to help themselves

25% of patients living with epilepsy have a learning disability.[22]

People with epilepsy who also have a learning disability can struggle to understand complex medical information. A few simple adjustments to your clinic's usual practice could make all the difference to these people, and empower them to understand their own health.

Keeping in regular contact

Some patients may struggle with a titration period of 10 weeks or more. Regular catch-ups can help by checking adherence to medication, monitoring for side effects, reviewing results, and addressing any questions they may have.

Helping your patients get the most out of their appointments

- Provide pens and paper, should patients wish to **make notes** during appointments
- Invite patients to **record** their appointments on their phones
- **Check understanding**: ask your patient to **repeat back to you the key points of the appointment**; add any important points that they may have missed
- Encourage patients to ask any questions they may have

Ensuring your patient feels confident about taking ONTOZRY®

- **Add some fun**: for patients who enjoy working towards goals, suggest and agree on some realistic goals to help keep them **motivated**. Goals can start small and be focused on healthy habits, such as completing the titration without missing a day of medication, or finishing the glass of water with the medication. Goals can also centre around regaining control of normal life, such as travelling on public transport alone or going out to meet friends
- Have your patient **agree on a set time** to take their tablet
- Provide the **Your ONTOZRY® Titration Diary** and encourage use during appointments
  - Check to see if patients have a **family member** or **someone they live with** who can help them record seizure details

Tools for patients

To help your patients learn more about their condition, the following key patient resources are available to HCPs to distribute to patients **once they have been prescribed ONTOZRY®**:

ONTOZRY® Patient Support Guide

A key resource for all patients receiving ONTOZRY®

Supports with titration, frequently asked questions (FAQs), and getting the most out of their appointments

Your ONTOZRY® Titration Diary

Supporting your patients through titration

A diary to help patients track adherence and record any seizures and side effects/symptoms

Check that your patients have the **ONTOZRY® Patient Support Guide** as a minimum and recommend the **Your ONTOZRY® Titration Diary. HCPs can order these resources from their local Angelini Epilepsy Account Specialist.**

Epilepsy organisation websites in the UK and Ireland

For patients eager to learn more about epilepsy, direct them to the patient-oriented websites below:

Websites in the UK:

- **Epilepsy Society***
  www.epilepsysociety.org.uk
- **Epilepsy Action***
  www.epilepsy.org.uk
- **Epilepsy Research***
  www.epilepsyresearch.org.uk

Websites in Ireland:

- **Epilepsy Ireland***
  www.epilepsy.ie
- **Epilepsy Care Foundation***
  www.epilepsycare.ie

Patient support programme

The patient support programme is for adults who are currently prescribed ONTOZRY® and has been designed to provide information and support throughout their treatment journey. It was developed by Angelini Pharma in partnership with Epilepsy Action UK.

It includes educational modules to help patients and their caregivers understand the condition and its treatment, as well as access to trained helpline advisers to answer their questions and provide wellbeing support at every stage of treatment.

* The content of independent patient organisations is not affiliated with Angelini Pharma or ONTOZRY®.

Responding to patients' FAQs

Patients have been provided with answers to commonly asked questions about taking ONTOZRY®, including side effects, and practical use in their **Support Guide**. The key points for each FAQ provided below help to reinforce key information for patients, who have been encouraged to discuss any further queries or concerns with their healthcare team. You can also refer patients to their Patient Information Leaflet for further information.

Remember: patients' questions may reflect an **underlying concern** that could impact their adherence. Try to explore why the question is important to them. Use our 'CHECK' questions to help you.

Taking ONTOZRY®

Patient FAQ	Key points
How long should I take my tablets for? FACT During the OLE of the pivotal 017 study, the discontinuation rate was 29% at 2 years[14]	Remind patients: ◦ ONTOZRY® is a long-term treatment ◦ However, your healthcare team may stop or change your dose of ONTOZRY® in the future if your circumstances change (for example if you find out you are pregnant or change to another medication) or if you can't tolerate it. This is why it is very important you tell your healthcare team of any changes in your health or how you feel ◦ **Adherence** is important
Can I stop taking ONTOZRY®?	**CHECK**: Do you want to stop taking ONTOZRY®? Why? ◦ **You should not change the dose or stop taking ONTOZRY®** without speaking to your HCP. If you and your HCP decide that ONTOZRY® is no longer right for you, it is recommended that you discontinue ONTOZRY® **gradually** to minimise the potential for rebound seizures (i.e. over at least 2 weeks), unless **safety concerns** require abrupt withdrawal
Can I take ONTOZRY® with my other epilepsy medications? FACT Around 20% of patients with epilepsy are receiving combination therapy[10] Refer to **Section 2 — Considerations for prescribers** for potential drug–drug interactions	**CHECK**: Have you stopped or started taking any other medications since you started taking ONTOZRY®? ◦ Some epilepsy medications don't have any effect on ONTOZRY®; other epilepsy medications may mean you can't have quite as high a dose or need a bit more monitoring ◦ When you were prescribed ONTOZRY®, your HCP will have carefully checked the medications you are on, to make sure it is safe to use. Refer patients to their Patient Information Leaflet for further information ◦ Emphasise the importance of adhering to both ONTOZRY® (as an **adjunctive**) and the need to take it alongside their usual epilepsy medicines
Is ONTOZRY® addictive? FACT To date, there are no reports of misuse, abuse or diversion[23]	Currently there is no evidence of ONTOZRY® causing dependency or addiction to taking it.
What if I forget to take ONTOZRY®? FACT Almost 50% of patients forget to take their medication at least once a month[24]	**CHECK**: How often do you forget to take ONTOZRY®? Remind patients that missing a dose can increase the **risk of having seizures**. 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. Give advice on how to build a good habit.
What if I take too much ONTOZRY®? FACT Medication overdoses are the most common type of poisoning in the UK[25]	Encourage patients to contact their doctor, nurse or pharmacist in the event of an overdose. Symptoms of overdose are expected to be consistent with the known adverse reactions of ONTOZRY® and include **somnolence**, **fatigue** and **dizziness**. There is no available specific antidote to the effects of ONTOZRY®. General supportive care of the patient is indicated, including monitoring of vital signs and observation of the clinical status of the patient. Suggest a **medication reminder** to help patients keep track of their dose.

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

The effects of ONTOZRY®

Patient FAQ	Key points
Is it ok to take ONTOZRY® if I'm pregnant? FACT Around 1 in every 3 women with epilepsy have an increase in seizures during their pregnancy[26]	◦ ONTOZRY® is not recommended in pregnancy or in women who are breastfeeding. ONTOZRY® should not be used during pregnancy unless the clinical condition of the woman requires treatment with ONTOZRY®

Looking after your medicine

Patient FAQ	Key points
How should I store my medication?	◦ There are no special storage conditions. To support patients, suggest keeping their epilepsy medication together in a place where it helps remind them to take their medication, but out of the reach and sight of children. Remind them to make sure they can easily identify each one

Other FAQs

Patient FAQ	Key points
Do I need an EEG or MRI? Refer to NICE pathways for detailed guidance[27]	◦ Ensure the patient understands that EEG and/or MRI scans are not treatments and therefore not required as standard for ONTOZRY® treatment ◦ Reinforce importance to continue taking ONTOZRY® as directed ◦ Check that adherence is not a challenge for the patient
I am going on holiday. Can I take my medication abroad? FACT: A small study suggested that air travel may increase seizures for patients with a prior history of flight-related seizures[28]	◦ It may be useful to enquire about holiday plans • Ensure patients have enough medication for the duration of their holiday • Advise patients to always carry their medication in its original packaging (unless in a dosette box), in their hand luggage, together with a copy of their prescription

If you require further information, please contact your local Angelini Epilepsy Account Specialist.

Interested to learn more?

Companion HCP websites to patient websites in the UK:*

- **Epilepsy Society**
  https://epilepsysociety.org.uk/what-we-do/information-professionals
- **Epilepsy Action**
  https://www.epilepsy.org.uk/professional

Companion HCP websites to patient websites in the UK and Ireland:*

- **SUDEP Action**
  https://sudep.org/

For more information on ONTOZRY®, scan below

https://www.harmoniamentis.co.uk/

* The content of independent patient organisations is not affiliated with Angelini Pharma or ONTOZRY®.

Professional organisations†

- The **Association of British Neurologists** (ABN) offers support, training, development and networking opportunities to neurologists in the UK and Ireland
- The **International League against Epilepsy** (ILAE) is the professional organisation representing all those interested in the field of epilepsy
- **Epilepsy Nurses Association** (ESNA) is the national professional organisation for all nurses supporting people with epilepsy. Its aims include promoting nursing research and development in order to improve care for those with epilepsy, and supporting nurses working in the field of epilepsy

† The content of independent professional organisations is not affiliated with Angelini Pharma or ONTOZRY®.

References

1. ONTOZRY® Summary of Product Characteristics. United Kingdom and European Union.
2. Scott AJ, *et al. Epilepsia.* 2017;58(6):973–982.
3. Anderson LL, *et al. Epilepsia.* 2014;55:1274–1283.
4. Piredda SG, *et al. The Journal of Pharmacology and Experimental Therapeutics.* 1985;232:741–745.
5. Stafstrom CE. *Epilepsy Currents.* 2007;7:15–22.
6. Vreugdenhil M, *et al. European Journal of Neuroscience.* 2004;19:2769–2778.
7. White HS, *et al. Epilepsy Research.* 1997;28:167–179.
8. Kwan P and Brodie MJ. *New England Journal of Medicine.* 2000;342:314–319.
9. Kwan P, *et al. Epilepsia.* 2010;51:1069–1077.
10. Chen Z, *et al. JAMA Neurology.* 2018;75:279–286.
11. NICE Technology appraisal guidance. TA753. Cenobamate for treating focal onset seizures in epilepsy. Published: 15 December 2021. Last updated: 6 May 2025. Available from: www.nice.org.uk/guidance/ta753. Last accessed May 2025.
12. Scottish Medicines Consortium. Cenobamate 12.5mg, 25mg, 50mg, 100mg, 150mg, and 200mg film-coated tablets (ONTOZRY®). https://scottishmedicines.org.uk/media/6671/cenobamate-ontozry-final-jan-2022-amended-180122-for-website.pdf. Last accessed May 2025.
13. Krauss GL, *et al. The Lancet Neurology.* 2020;19:38–48.
14. Klein P, *et al. Neurology.* 2022;99(10):e989–e998.
15. Chung SS, *et al. Neurology.* 2020;94:e2311–2322.
16. French JA, *et al. Epilepsia.* 2021;62:2142–2150.
17. Sperling MR, *et al. Epilepsia.* 2020;61:1099–1108.
18. Yeh MY, *et al. Applied Nursing Research.* 2018;39:11–17.
19. Davis KL, *et al. Epilepsia.* 2008;49:446–454.
20. Jones RM, *et al. Seizure.* 2006;15:504–508.
21. Tang F, *et al. Epilepsy & Behavior.* 2013;27:85–89.
22. Shankar R, *et al. PLoS ONE.* 2018;13(6):e0198261.
23. Abdul Rahim MI, Thomas RH. Gamification of Medication Adherence in Epilepsy. Seizure. 2017 Nov;52:11-14. https://www.seizure-journal.com/article/S1059-1311(17)30529-0/fulltext. Last accessed May 2025.
24. Epilepsy Research UK 2017. Poll shows that almost 50% of people forget to take their medication at least once a month. https://epilepsyresearch.org.uk/poll-shows-that-almost-50-of-people-forget-to-take-their-medication-at-least-once-a-month/. Last accessed May 2025.
25. NHS 2018. Symptoms. Poisoning. https://www.nhs.uk/conditions/poisoning/symptoms/. Last accessed May 2025.
26. Epilepsy Action 2020. During pregnancy. https://www.epilepsy.org.uk/info/daily-life/having-baby/pregnancy. Last accessed May 2025.
27. National Institute for Health and Care Excellence 2021. Epilepsy overview. https://pathways.nice.org.uk/pathways/epilepsy. Last accessed May 2025.
28. Trevorrow T. *Seizure.* 2006;15:320–327.

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