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ONTOZRY▼ cenobamate

Angelini Pharma

THINK SEIZURE FREEDOM*

Every Seizure Matters

▼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 email to: UKIReporting@angelinipharma.com.

Indication (UK): 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 (ROI): 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]

*Seizure freedom was a secondary endpoint in the C017 pivotal study. The primary endpoint was the percentage of patients achieving 50% reduction from baseline in focal seizure frequency during the 12-week maintenance. High rates of sustained seizure freedom were observed in the C017 study. Seizure frequency reductions of 100% during the 12-week maintenance phase were 1% (n=1/102) for the placebo group, 4% (n=4/102) for the ONTOZRY® 100 mg/day group, 11% (n=11/98; p=0.0022) for the ONTOZRY® 200 mg/day group and 21% (n=20/95; p<0.0001) for the ONTOZRY® 400 mg/day group.[2]

Co-medication management is needed to maximise cenobamate effectiveness while maintaining tolerability[3]

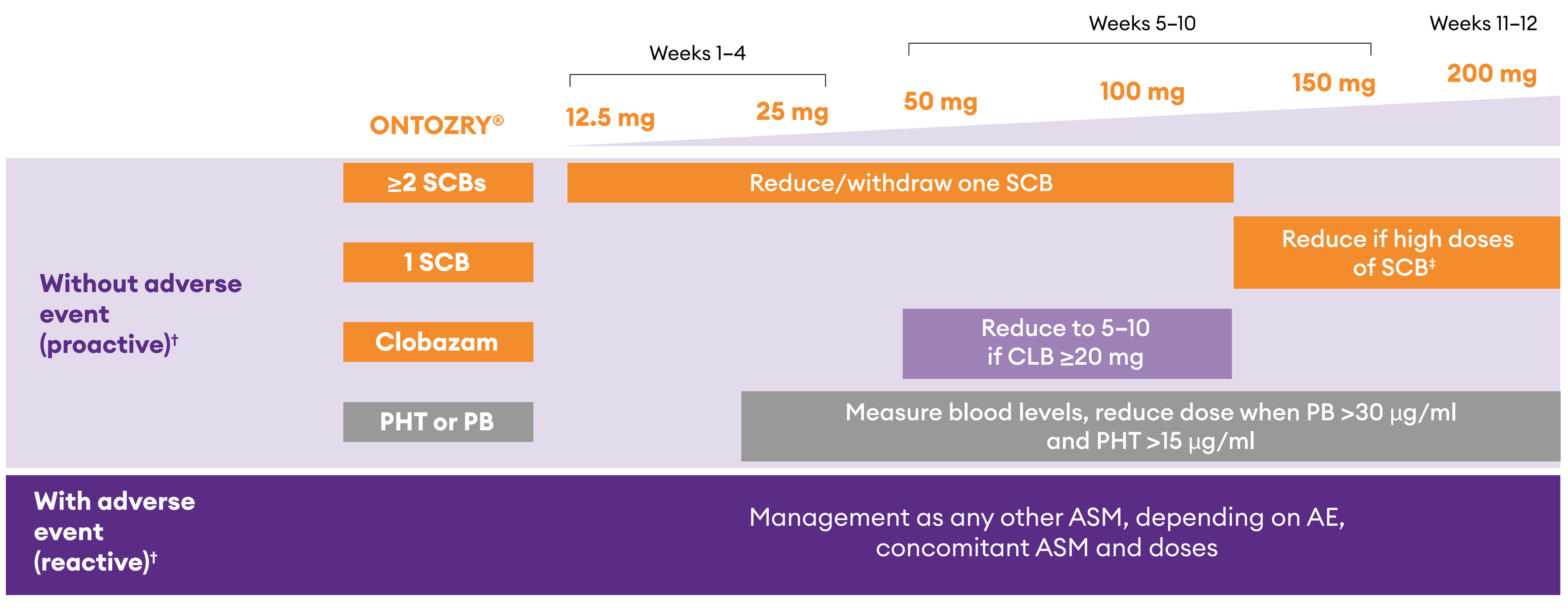
Dose adjustments should be made on a case-by-case basis, bearing in mind the concomitant ASM doses, seizure type and frequency, tolerability to ASMs, and comorbidities[3]

No dose adjustments are needed with many concomitant ASMs[1]

	Adding ONTOZRY® may require the following dose adjustments:
Carbamazepine	None required.
Lacosamide	None required.
Levetiracetam	None required.
Oxcarbazepine	None required.
Valproic acid	None required.
Clobazam	↓ Decrease dose of clobazam.
Phenobarbital	↓ Decrease dose of phenobarbital depending on individual response (monitor phenobarbital levels during ONTOZRY® titration).
Phenytoin	↓ Decrease dose of phenytoin depending on individual response (monitor phenytoin levels during ONTOZRY® titration).
Lamotrigine	↑ Increase dose of ONTOZRY® depending on individual response.

Please see the Summary of Product Characteristics for further information on management of drug-drug interactions.

Drug load reduction of other ASM[3]


Weeks 1–4
Weeks 5–10
Weeks 11–12
ONTOZRY®
12.5 mg
25 mg
50 mg
100 mg
150 mg
200 mg
Without adverse event (proactive)†
≥2 SCBs
Reduce/withdraw one SCB
1 SCB
Reduce if high doses of SCB‡
Clobazam
Reduce to 5–10 if CLB ≥20 mg
PHT or PB
Measure blood levels, reduce dose when PB >30 µg/ml and PHT >15 µg/ml
With adverse event (reactive)†
Management as any other ASM, depending on AE, concomitant ASM and doses

Please consult the Summary of Product Characteristics for further information.

Adapted from Figure 2 and text in Carreño M, et al. 2024.
†On a case-by-case basis, considering type of ASM, doses, blood levels, tolerability to ASMs, patients' comorbidities, disease severity, type and frequency of seizures.[3]
‡Carbamazepine ≥800 mg/day, oxcarbazepine >900 mg/day, eslicarbazepine >1200 mg/day, lacosamide >300 mg/day, and lamotrigine >300 mg/day.[3]

Interactions with Oral Contraceptives and CYP substrates[1]

	Adding ONTOZRY® may require the following dose adjustments:
Oral contraceptives	**ONTOZRY® 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 ONTOZRY® and until 4 weeks after treatment discontinuation.
CYP3A4 substrates (eg., midazolam)	↑ Increase dose of medicines metabolised by CYP3A4.
CYP2B6 substrates (eg., bupropion)	↑ Increase dose of medicines metabolised by CYP2B6.
CYP2C19 substrates (eg., omeprazole)	↓ Decrease dose of medicines metabolised by CYP2C19.

Cenobamate is an effective adjunctive ASM with a dose-dependent effect[1,2]

The recommended starting dose of cenobamate is **12.5 mg/day**, titrated gradually to the recommended **target dose of 200 mg/day**[1]

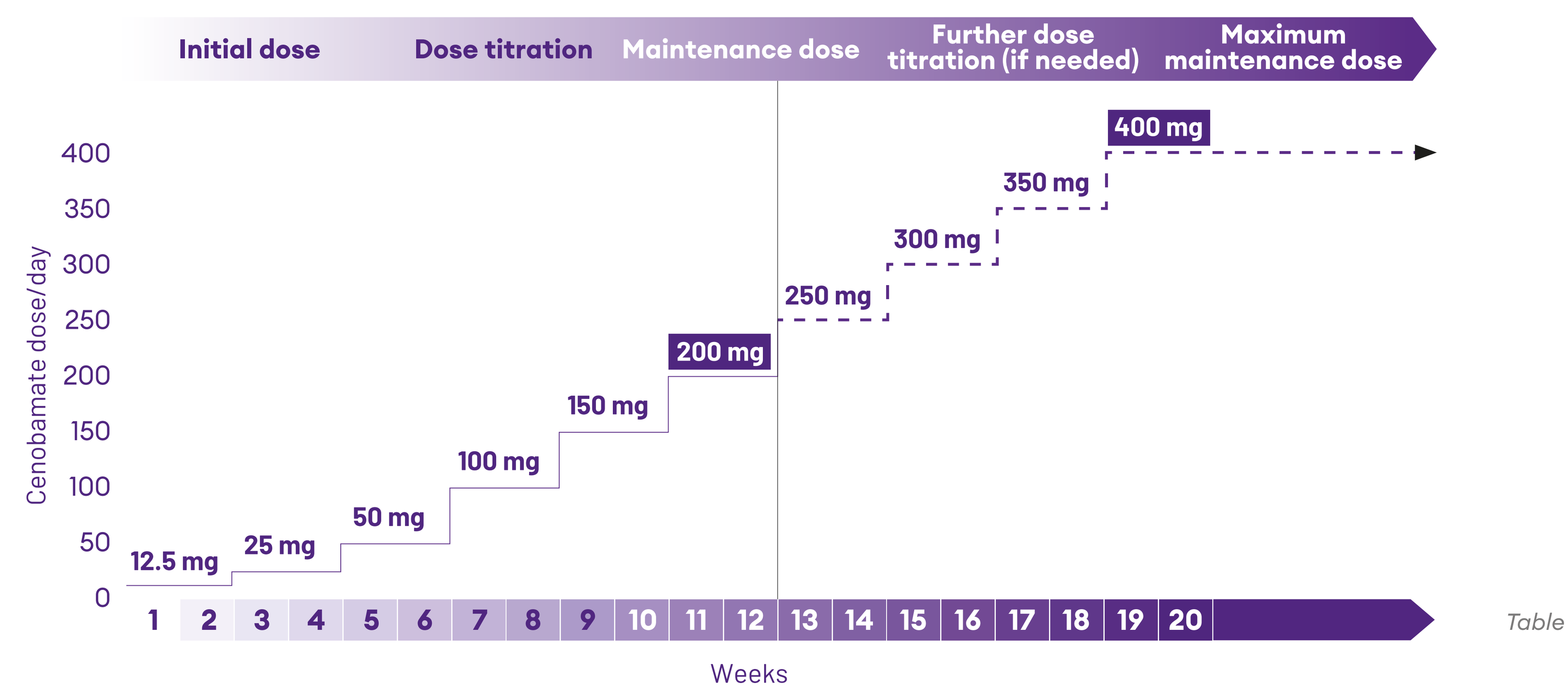

Initial dose
Dose titration
Maintenance dose
Further dose titration (if needed)
Maximum maintenance dose
Cenobamate dose/day
400
350
300
250
200
150
100
50
0
12.5 mg
25 mg
50 mg
100 mg
150 mg
200 mg
250 mg
300 mg
350 mg
400 mg
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Weeks

Table 1, Ref.2

Some patients, **who do not reach optimal seizure control,** may **benefit from doses above 200 mg** (increased by increments of 50 mg/day every 2 weeks) up to a maximum of 400 mg/day[1]

Open and regular communication between the patient and provider is critical to improve adherence[4]

THINK SEIZURE FREEDOM

EVERY SEIZURE MATTERS

- The probability of achieving **seizure freedom diminishes sharply with each unsuccessful ASM regimen** and, **after 2 ASMs, it does not differ significantly** with each successive ASM regimen[5]

THINK EFFICACY

- With ADJUNCTIVE ONTOZRY®, nearly one quarter of the patients (22.1%) **sustained seizure freedom after 2.5 years**[6]
- Results from a recent **real-world study** were **consistent with those observed in randomised clinical trials → 42.0%** of patients reported a **≥75% reduction** in baseline seizure frequency and **20.2% achieved seizure freedom**[7]
- In an Irish EAP, **67.4% of the responders** were treated with **ONTOZRY® doses of ≥250 mg/day.**[8] The recommended target dose is 200 mg/day[1]

THINK TOLERABILITY

- **In a multicenter, retrospective evaluation of real-world clinical practice, adverse events were manageable**[9]
- The **most commonly reported adverse reactions** were somnolence, dizziness, fatigue and headache[1]

THINK SIMPLICITY

- Adding ONTOZRY® led to **reduced mean concomitant ASM drug loads, regardless of ASM drug class**[10] **→ 59.2%** of patients were able to **reduce or withdraw one or more concomitant ASMs** in a real-world analysis[7]

ONTOZRY® cenobamate

AE, adverse event; ASM, anti-seizure medication; CLB, clobazam; DRE, drug-resistant epilepsy; ECG, electrocardiogram; PB, phenobarbital; PHT, phenytoin; SCB, sodium channel blocker; TEAEs, treatment-emergent adverse events.

References:
1. ONTOZRY® Summary of Product Characteristics. United Kingdom and European Union.
2. Krauss GL, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol.2020;19(1): 38–48.
3. Carreño M, et al. Spanish consensus on the management of concomitant antiseizure medications when using cenobamate in adults with drug-resistant focal seizures. Epilepsia Open. 2024;9(3):1051-1058.
4. Steinhoff BJ, et al. Therapeutic Strategies During Cenobamate Treatment Initiation: Delphi Panel Recommendations.
5. Chen Z, et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: A 30-year longitudinal cohort study. JAMA Neurol. 2018;75(3):279–86.
6. Vossler DG, et al. Sustainability of seizure reduction and seizure control with adjunctive cenobamate: Post hoc analysis of a phase 3, open-label study. Epilepsia. 2023;64(10):2644–52.
7. Pietrafusa N, et al. Cenobamate as add-on therapy for drug resistant epilepsies: effectiveness, drug to drug interactions and neuropsychological impact. What have we learned from real word evidence? Front Pharmacol. 2023;14:1239152.
8. Peña-Ceballos J, et al. Adjunctive cenobamate in highly active and ultra-refractory focal epilepsy: A "real-world" retrospective study. Epilepsia. 2023;64(5):1225–35.
9. Bosak M, et al. Efficacy and safety of Cenobamate: a multicenter, retrospective evaluation of real-world clinical practice. Seizure. 2025;130:25–31.
10. Aboumatar S, et al. Reductions in concomitant antiseizure medication drug load during adjunctive cenobamate therapy: Post-hoc analysis of a subset of patients from a phase 3, multicenter, open-label study. Epilepsy Res. 2024;200:107306.

Please consult the Summary of Product Characteristics for further information.

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