NHS
Pan Mersey
Area Prescribing Committee

CENOBAMATE tablets (Ontozry® ▼)
for treating focal onset seizures in adults with epilepsy

The Pan Mersey Area Prescribing Committee recommends the prescribing of CENOBAMATE tablets (Ontozry® ▼), following specialist initiation, for treating focal onset seizures in adults with epilepsy in accordance with NICE TA753.

AMBER following specialist initiation

NICE technology appraisal (TA753)[1] recommends cenobamate tablets (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-epileptic drugs. It is recommended only if:

- It is used as an add-on treatment, after at least 1 other add-on treatment has not controlled seizures, and
- Treatment is started in a tertiary epilepsy service

The NICE Clinical guideline (CG 137)[2] 'Epilepsies: diagnosis and management' recommends specific drugs for first line, adjunctive and tertiary use in focal epilepsy. The recommendation for cenobamate above would be in keeping with this existing guidance, with cenobamate being considered on referral to tertiary care.

NICE does not expect this guidance to have a significant impact on resources; that is, the resource impact of implementing the recommendations in England will be less than £5 million per year in England (or approximately £9,000 per 100,000 population). This is because cenobamate is a further treatment option, the overall cost of treatment will be similar and NICE does not think practice will change substantially as a result of this guidance. Short-term clinical evidence shows that cenobamate reduced the number of seizures and also increases how many people stop having any seizures. These benefits may result in capacity benefits from a reduction in administration and management costs.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

Cenobamate is a positive allosteric modulator of subtypes of the ɣ-aminobutyric acid ($GABA_A$) ion channel[3]. The precise mechanism of action by which cenobamate exercises their therapeutic effect in patients with focal-onset epilepsy is unknown.

Two multinational, multicentre, double-blind trials, C013 (1 cenobamate arm – 200mg once daily)[4] and C017 (3 cenobamate arms - 100mg, 200mg and 400mg, all once daily)[5]. The trials compared cenobamate with placebo in a total of 659 adults (aged 18 to 70) with drug resistance focal seizures despite treatment with at least 1 antiseizure medicine in the last 1-2 years, who had 1-3 concomitant medicines at baseline that continued during the trial. Both trials had 6-week titration periods, but C013 had a 6-week maintenance phase, compared with 12 weeks in C017. The primary end point of C013 was the percentage change from baseline in seizure frequency per 28 days in the treatment period. In C017, it was at least a 50% reduction in seizures from baseline during the maintenance period. The results showed that for this outcome, 25.5% of people in the placebo arm had at least a 50% reduction in seizure frequency compared with 40.2%, 56.1% and 64.2% in the 100mg, 200mg and 400mg arms respectively.

Two open-label extension, single arm studies provided longer term effectiveness and safety data. C017-OLE used 300mg cenobamate for 355 people who had completed the C017 trial. C021 is an ongoing phase 3, single arm, open-label, multinational, multicentre study including 1,347 people with drug resistant focal seizures[6]. Cenobamate doses from 200mg – 400mg were titrated over 12 weeks, followed by a 40-week maintenance period. The results showed that 23.2% of people were seizure free for at least 1 year during the C017-OLE study.

Safety

The most commonly reported adverse reactions were somnolence, dizziness, fatigue and headache[3]. The discontinuation rate because of adverse reactions in clinical trials were 5%, 6% and 19% for patients randomised to receive 100mg/day, 200mg/day and 400mg/day of cenobamate respectively, compared with 3% in patients randomised to receive placebo[3]. The adverse reactions most commonly leading to discontinuation were ataxia, dizziness, somnolence, nystagmus, vertigo and dipolopia. These were found to be dose dependent and the titration scheme should be strictly followed. It is recommended that discontinuation should be gradual to minimise the potential for rebound seizures (i.e. over at least 2 weeks), unless safety concerns require abrupt withdrawal[3].

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications[3]. Drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, has been reported with cenobamate use when started at higher doses and titrated rapidly[3]. QT-shortening has also been observed the cenobamate use and caution is required when prescribing cenobamate with other QT-shortening drugs[3].

Contraindications include hypersensitivity to the active substance or excipients and familial short-QT syndrome. For further details on safety, drug interactions, cautions and contraindications please see SPC[3].

Cost

One year at recommended maintenance doses of cenobamate costs £2690[3].

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Patient factors

Patients aged 65 and over were not included in sufficient numbers in clinical studies. Lower starting doses may be required[1]. Use with caution and reduction of the target dose may be considered in patients with mild to moderate (CrCl 30 to <90ml/min) or severe (CrCl < 30ml/min) renal impairment[1]. The maximum recommended dose for patients with mild to severe renal impairment is 300mg/day[1]. Cenobamate should not be used in patients with end-stage renal disease. A decreased target dose of up to 50% may be required in patients with chronic hepatic disease[3]. The maximum recommended dose in patients with mild to moderate hepatic impairment is 200mg/day[3]. Cenobamate should not be used in patients with severe hepatic impairment[3].

There is no adequate data on the use of cenobamate in pregnant women. Cenobamate is not recommended in

women of child bearing potential not using contraception. Women of child bearing potential using oral contraceptives should also be advised to use additional or alternative non-hormonal form of contraception during treatment and until 4 weeks after treatment is discontinued. It is unknown whether cenobamate or its metabolites are secreted in human milk. For further details on cenobamate use in pregnancy and breastfeeding, please see SPC .

Prescribing information

The recommended starting dose of cenobamate is 12.5mg per day, titrated gradually to the recommended target dose of 200mg per day[1]. Based on clinical response, dose may be increased to a maximum of 400mg per day[3].

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: patients should be advised to take a single missed dose as soon as they remember unless it is less than 12 hours until the next regularly scheduled dose[3].

Treatment cessation: if cenobamate is to be stopped, to prevent potential for rebound seizures, discontinuation should be gradual, unless safety concerns require abrupt withdrawal[3]. Tertiary centres will advise the patient's GP on cenobamate withdrawal where required.

Implementation notes

- Cenobamate requires specialist initiation in a tertiary epilepsy service by a consultant neurologist with appropriate experience in the treatment of drug resistant epilepsy.
- Patients will be counselled by the specialist service regarding signs and symptoms of DRESS on initiation and advised to monitor closely for skin reactions.
- Prescribing is to be continued by the specialist until stabilisation of the dose and the patient's condition is achieved, and the patient has been reviewed by the specialist. The specialist may then request the patient's GP to take over prescribing responsibilities of treatment.

References

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4. Chung S, French J et al. Randomised Phase 2 Study of Adjunctive Cenobamate in Patients With Uncontrolled Focal Seizures.Neurology. June 02,2020; 94(22)
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6. Ferrari Louis, Rosenfeld W et al. Long Term Efficacy of Cenobamate by Concomitant Antiseizure Mediation: Post-hoc Analysis of the C017 Open-label Extension Study. Neurology. April 13, 2021;96