AMBER 2 GUIDANCE FOR CENOBAMATE

1. Background

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.

In Hull, East Riding of Yorkshire, North Lincolnshire and North East Lincolnshire cenobamate is classified as an Amber 2 medication and can be prescribed by GPs following initiation and stabilisation by the tertiary epilepsy service.

2. Indication

Cenobamate is for the adjunctive treatment of focal seizures with or without secondary generalisation in adults with epilepsy not adequately controlled despite treatment with at least two anti-seizure medications.

3. Dose/Duration

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

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 dose3 . Treatment cessation: if cenobamate is to be stopped, to prevent potential for rebound seizures, discontinuation should be gradual, unless safety concerns require abrupt withdrawal. Tertiary centres will advise the patient's GP on cenobamate withdrawal where required.

Renal impairment

Cenobamate should be used with caution and reduction of the target dose may be considered in patients with mild to moderate (creatinine clearance 30 to <90 ml/min) or severe (creatinine clearance < 30 ml/min) renal impairment. The maximum recommended dose for mild, moderate, or severe renal impairment is 300 mg/day. Cenobamate should not be used in patients with end-stage renal disease or undergoing haemodialysis.

Hepatic impairment

Exposure to cenobamate was increased in patients with chronic hepatic disease. A change in the starting dose is not required; however, a reduction in target dose of up to 50% can be considered by the specialist, and 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.

Older people

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.

Preparations available

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

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

Cenobamate (Ontozry) 50 mg film-coated tablets- packs of 14, 28

Cenobamate (Ontozry) 100 mg film-coated tablets – packs of 14, 28

Cenobamate (Ontozry) 150 mg film-coated tablet – packs of 14, 28

Cenobamate (Ontozry) 200 mg film-coated tablets– packs of 14, 28

4. Contraindications

Hypersensitivity to the active substance or any excipients listed in section 6.1 of the SPC

Familial Short QT syndrome

Refer to the SPC for a full list of contraindications

5. Cautions

QT-shortening

A dose-dependent shortening of the QTc interval has been observed with cenobamate but not below 340 msec. There was no evidence that combining cenobamate with other antiseizure medicines led to further QT-shortening in clinical trials. Clinicians should use caution when prescribing cenobamate in combination with other medicinal products known to shorten the QT (e.g., propranolol) and consider ECG monitoring as appropriate.

Contains lactose

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

6. Clinical Monitoring

The specialist will arrange baseline blood tests (FBC, LFTs AND U&Es) and repeat these after three months of treatment with cenobamate if clinically indicated.

If deemed appropriate, an ECG at baseline may be requested by the specialist and repeated if necessary.

The specialist may conduct additional investigations as required, e.g., therapeutic drug levels of anti-seizure medication(s). The results will be sent to the GP. GPs will not be routinely expected to undertake blood monitoring (except in exceptional circumstances agreed with a GP on a case-by-case basis).

7. Adverse effects

Adverse effects	Action for GP
Drowsiness or fatigue	These symptoms should subside; however, the patient should be referred back to the specialist for evaluation if they persist.
Dizziness	If this occurs, the patient should be advised not to drive (if applicable) and not to use tools or machinery. If this does not subside, the patient should be referred to a specialist for evaluation
Headache	The patient should be advised to keep hydrated with water and rest. If the headache persists, this should be discussed with the specialist
Diplopia	If this persists the patient should be referred back to the specialist.

Uncommon serious side effects

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

DRESS, which can be life-threatening or fatal, has been reported associated with cenobamate when started at higher doses and titrated rapidly (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.

Symptoms of DRESS typically (although not exclusively) include fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. If signs and symptoms suggestive of this reaction appear, cenobamate should be withdrawn immediately, and the patient should attend their local emergency department. The specialist should be informed of this. 1

- Suicidal Behaviour and Ideation

There have been reports of suicidal ideation and behaviour with anti-seizure agents in several indications. This risk mechanism is unknown, and the available data do not exclude the possibility of an increased risk for cenobamate. Patients should be monitored for signs of suicidal ideation & behaviour and should be advised to seek medical advice if signs emerge during treatment.

- In case of an allergic reaction, cenobamate should be immediately discontinued, and the consultant and/or specialist nurse should be informed

For a full list of adverse effects, refer to the Summary of Product Characteristics: Ontozry 200 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Cenobamate is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

8. Drug interactions

The following drugs are known or suspected interactions:	
Interacting Drug	Advice
Oral contraceptives	Since CYP3A4 may also metabolise hormonal contraceptives, their efficacy may be reduced by concomitant use with cenobamate. Therefore, women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal birth control measures
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.
Phenytoin	Cenobamate exposure may be reduced and phenytoin exposure may be increased. No dose adjustment of cenobamate is required. Phenytoin levels should be monitored during titration of cenobamate, and based on individual response the dose of phenytoin may need to be reduced.
Phenobarbital	No dose adjustment of cenobamate is required. Concentrations of phenobarbital should be monitored during cenobamate titration, and based on individual response, the dose of phenobarbital may need to be reduced.
Clobazam	No dose adjustment of cenobamate is required. Due to a possible increase in exposure of the active metabolite of clobazam (N-desmethylclobazam), related to the induction of CYP3A4 (formation) and the inhibition of CYP2C19 (elimination), the dose of clobazam may need to be reduced
Lamotrigine	Pharmacometric analyses of data from healthy subjects and patients showed that concomitant administration of cenobamate with lamotrigine did not affect cenobamate exposures. Still, they resulted in dose-dependent decreases in lamotrigine concentrations. Based on subpopulation analyses of patients taking concomitant lamotrigine, higher doses (200 - 400 mg/day) of cenobamate may be required for efficacy when co-administered with lamotrigine. Depending on individual response, the dose of cenobamate may need to be increased
Cenobamate may reduce exposures of products primarily metabolized by CYP3A4 (e.g. buspirone, sirolimus, tacrolimus,) and CYP2B6 (e.g. bupropion).	
Cenobamate may increase exposures of products primarily metabolized by CYP2C19 (e.g. omeprazole	
In vitro studies have shown exposure of medicinal products transported by OAT3 (e.g empagliflozin, sitagliptin) may also be increased	
When initiating or discontinuing treatment with cenobamate or changing the dose, it may take two weeks to reach the new level of enzyme activity.	

9. Pregnancy and Lactation

There is no adequate data for the use of cenobamate in pregnant women. Women of childbearing potential must use effective contraception during cenobamate treatment and until four weeks after treatment discontinuation. The efficacy of hormonal contraceptives may be reduced by concomitant use with cenobamate. Therefore, women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal birth control measures

10. Information for patient

Patients will be provided with information on titrating dose and any changes to other antiepileptic dosages. Patients will be counselled on adverse effects.

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.

Patients will be advised to report any adverse effects via the yellow card scheme.

Document and version control	**This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.**		
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