North Central London
Joint Formulary Committee

Shared Care Guideline

Treatment of focal seizures with cenobamate

Dear GP

The information in the shared care guideline has been developed in consultation with Primary Care, and it has been agreed that it is suitable for shared care.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the Consultant when treatment is initiated. It is important that patients are consulted about treatment and are in agreement with it.

Contents

1. Introduction

This document provides information on clinical and legal responsibility for prescribing this drug.

Cenobamate is an anti-seizure medication developed to treat focal epileptic seizures.[1] The precise mechanism of action by which cenobamate exercises its therapeutic effects is unknown, although an effect on both GABA and sodium channels has been proposed. [1]

Cenobamate is on the NCL Joint Formulary as an option for treating focal seizures with or without secondary generalisation in adults with drug-resistant epilepsy not adequately controlled having tried at least two antiseizure medications (see NICETA753). [2] It is recommended only to be used as an adjunctive treatment, after at least one other add-on treatment has not controlled seizures.[2]

Progressing to a stable, optimal dose usually takes approximately 11 weeks. Once achieved, a shared care arrangement with you will be requested. This will clarify responsibilities between the specialist and general practitioner (GP) for managing the prescribing of cenobamate such as:

- Who will prescribe
- Who will monitor
- Any tests required (e.g., blood tests), the exact names/nature of the tests, why they are needed, the frequency of testing, the location in which these will be carried out, and action to be taken for any abnormal results
- Which clinician will be responsible for receipt and review of the results
- Who will communicate any necessary changes in dose to the patient and the GP

2. Shared Care criteria

Patients established on cenobamate and appropriately monitored at baseline and after initiation of treatment with no problems identified during this period.

Abbreviations

ECG: Electrocardiogram

FBC: Full Blood Count

LFT: Liver Function Test

U&Es: Urea and electrolytes

3. Shared care responsibilities

3.1. Consultant and /or Specialist Nurse

Send a letter to the GP along with shared care criteria and transfer form requesting shared care for this patient.: indication, dose and frequency to be decided by the hospital team.

1) Before initiating treatment, perform a baseline test to measure LFTS, U&Es and FBC. An ECG at baseline may be taken if deemed appropriate.
2) Discuss the benefits and side effects of treatment with the patient. Provide the patient with a Patient Information leaflet, and ensure that the patient understands the treatment and dosing regimen.
3) Initiate treatment and prescribe until the GP formally agrees to share care (until the patient is stabilised or as according to Section C for local minimum supply durations). Patients will be seen in the clinic before consideration of shared care
4) Discuss the shared care arrangement with the patient.
5) Provide results of baseline tests and recommend the frequency of monitoring to GP. The consultant must also explain what the recommended tests are, why they are needed and the location in which these tests will be carried out

6) Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results, and frequency of monitoring are stated
7) Inform GP of blood test results, actions to take in case of abnormal results, and advise the GP on when to adjust the dose, stop treatment, or consult with a specialist
8) Periodically review the patient's condition and communicate promptly with the GP when treatment is changed. Counsel the patient on any dose changes that are made during clinic appointments
9) Evaluate adverse effects reported by GP or patient
10) Report adverse events to the MHRA (via yellow card scheme) and GP
11) Inform GP of patients who do not attend clinic appointments
12) Ensure that precise backup arrangements exist for GPs to obtain advice and support

3.2. General Practitioner

Complete transfer form and send back to h*ospital* confirming acceptance/ rejection of shared care for a patient. If the GP cannot agree to shared care, inform the Hospital team stating reasons within ***14 days*** of the request. If no response is received within 14 days, the Consultant will assume the GP has accepted shared care.

1) Monitor patient's overall health and well-being
2) Prescribe the medication as described (but not alter the dose unless advised to do so by the specialist). The term "as directed" **SHOULD NOT** be used
3) Ensure that the patient understands the dosing
4) Ensure the patient understands that they must report the warning symptoms as listed under "adverse effects"
5) Ensure compatibility with concomitant medication. Please see the drug interactions section.
6) Monitor results at recommended frequencies as described under "clinical monitoring" and inform the Consultant if abnormal.
7) Adjust the dose as advised by the specialist (where applicable) and counsel the patient on any dose changes
8) Report any adverse events and non-compliance to the hospital specialist, where appropriate
9) Stop treatment on the advice of a specialist or immediately if clinically urgent
10) Help in monitoring the clinical progression and inform the hospital team of any changes to medication or condition
11) Report adverse events to the specialist and MHRA
12) All requests for repeat prescriptions should be reviewed individually before issuing

3.3. Patient responsibility

1) Attend all hospital and GP appointments
2) Take medicines as agreed
3) Report to the specialist or GP if they do not have a clear understanding of the treatment
4) Inform specialist or GP of any other medication being taken, including over-the-counter products
5) Report any adverse effects or warning symptoms to GP or specialist
6) Inform hospital and GP of any changes in address or telephone numbers

3.4. Clinical Commissioning Group

1) To provide feedback to Trusts from the standard letter via the shared care forum.
2) To support GPs in deciding whether to accept clinical responsibility for prescribing.
3) To support Trusts in resolving issues that may arise due to shared care.

4. Indications

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.

5. Dose and Administration

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

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.	

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.[1]

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. [1]

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.[1]

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

6. Adverse effects

Possible adverse effects and what to do if they occur:

The most commonly reported adverse reactions were drowsiness, dizziness, fatigue and headache. [1]

- 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. [1]

  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)

Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the CHM.

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.

7. Cautions

Women of childbearing potential
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.

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.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 6)

Suicidal Behaviour and Ideation (see section 6).

8. 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).

9. Contraindications

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

Familial Short-QT syndrome

Refer to the Summary of Product Characteristics for a full list of contraindications.

10. Drug Interactions

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.

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. [1]

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. [1]

Interactions with other antiepileptics

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. [1]

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. [1]

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. [1]

Carbamazepine

A study in healthy subjects, showed no significant change in the exposure of cenobamate. Still, carbamazepine exposures were slightly reduced. No clinically meaningful decreases in efficacy were observed in subpopulation analyses of patients taking concomitant carbamazepine. Therefore, no dose adjustments are required. [1]

Valproic acid

Pharmacometric analyses of data from healthy subjects and patients indicated that concomitant administration of cenobamate with valproic acid did not affect cenobamate exposures and had no clinically relevant reductions in valproic acid concentration. No dose adjustments are required. [1]

Lacosamide, levetiracetam and oxcarbazepine

Pharmacometrics analyses of data from healthy subjects and patients indicated that concomitant administration with lacosamide, levetiracetam, or oxcarbazepine did not affect the exposure of cenobamate, and cenobamate did not have a clinically relevant effect on exposures of lacosamide, levetiracetam, or oxcarbazepine. No dose adjustments are required for cenobamate, lacosamide, levetiracetam, or oxcarbazepine. [1]

For further information regarding drug interactions, refer to the Manufacturers Summary of Product Characteristics, BNF, or the most up to date version of Stockleys' Drug Interactions.

11. References

Arvelle Therapeutics UK. Summary of Product characteristics. Ontozry 200mg film coated tablets. Date accessed 08/03/22. https://www.medicines.org.uk/emc/product/13012/smpc

NICE. Cenobamate for treating focal onset seizures in epilepsy-Technology appraisal guidance [TA753]Published: 15 December 2021. Date accessed 08/02/22. Overview | Cenobamate for treating focal onset seizures in epilepsy | Guidance | NICE.

FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Date accssed 03/10/2020.https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3.

12. Contact Details

National Hospital for Neurology and Neurosurgery

Hospital switchboard:	020 3448 1901
Consultants: **Dr Sanjeev Rajakulendran** **Prof Ley Sander**	020 3448 8609
Epilepsy Nurse specialists	020 3448 8627
Specialist or Dept Pharmacist: NHNN Pharmacy/ Lindsey Stockford	ext / 83140

Royal Free London

Hospital switchboard:	020 7794 0500
Consultants: **Dr Heather Angus-Leppan** **Dr Rebecca Liu**	(Clinical Pathway Administrator: Ext: 34365 020 7830 2864
Epilepsy Nurse specialists	Joana Popo (Ext: 36113, M: 07985 360348)
Specialist or Dept Pharmacist:	Huei Ling Yeoh (Bleep 2750, E: huei.yeoh@nhs.net)

North Middlesex University Hospital

Hospital switchboard:	020 8887 2000
Consultants: **Dr Sanjeev Rajakulendran**	0208 887 2444 northmid.neurology@nhs.net

Document control

Date	Version	Amendments
24/08/2022	1.0	New shared care document
03/03/2023	1.1	Updated with NMUH contact information

Groups / Individuals who have overseen the development of this guidance:	Ms Lindsey Stockford Prof. Ley Sander Dr. Sanjeev Rajakulendran Ms Sasha Monaghan Ms Evelyn Frank Ms Marwa Awadi Dr Dominic Roberts
Groups which were consulted and have given approval:	NCL consultants and specialist pharmacists NCL Shared Care Group
File name:	SCG_Cenobamate
Version number:	1.1
Available on:	www.ncl-mon.nhs.uk
Disseminated to:	NCL formulary pharmacists and commissioners
Equality impact assessment:	Low
NCL Shared Care Group Approval date:	03/03/2023
Review date:	25/08/2025

Appendix 1: Cenobamate transfer form: from [Trust] to GP practice

Section A: to be completed by secondary care *Send to practice*

This document is to request the shared care pathway of your patient and comprises an agreement betweer the GP and named consultant. The patient will continue to be seen by the named consultant as regular follo up.

Fix address label here (ensure NHS no.on)	Clinic stamp *or give details below*

Department			
Clinic phone			
Consultant		Email	
Indication for prescription			
Drug prescribed			
Date	Drug started	Current dose	
Relevant conditions			
Monitoring variations			
Date next blood test		Next disease review due in	months' time.

Section B: [Accept Shared Care] to be completed by practice *Send back **FAO referring consultant** above*

The above patient has been accepted into our monitoring service.

Practice date for next blood test		Practice stamp
Signed / Designation		
Date		

Section B: [Reject Shared Care] to be completed by practice *Send back **FAO referring consultant** above*

The above patient has not been accepted into our monitoring service.

Reason		Practice stamp
Signed / Designation		
Date		

Section C: Shared Care Agreement (Trust specific information)

This section (and reference to it: Consultant Shared Care Responsibilities point 3) can be removed if all Trusts and CCGs have the same contractual arrangements.

Contact details	
Clinic / service	
Address	
Email	
Telephone	

Contractual details

CCG 1	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	

CCG 2	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	

CCG 3	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	