## 1. Introduction and Who Guideline applies to

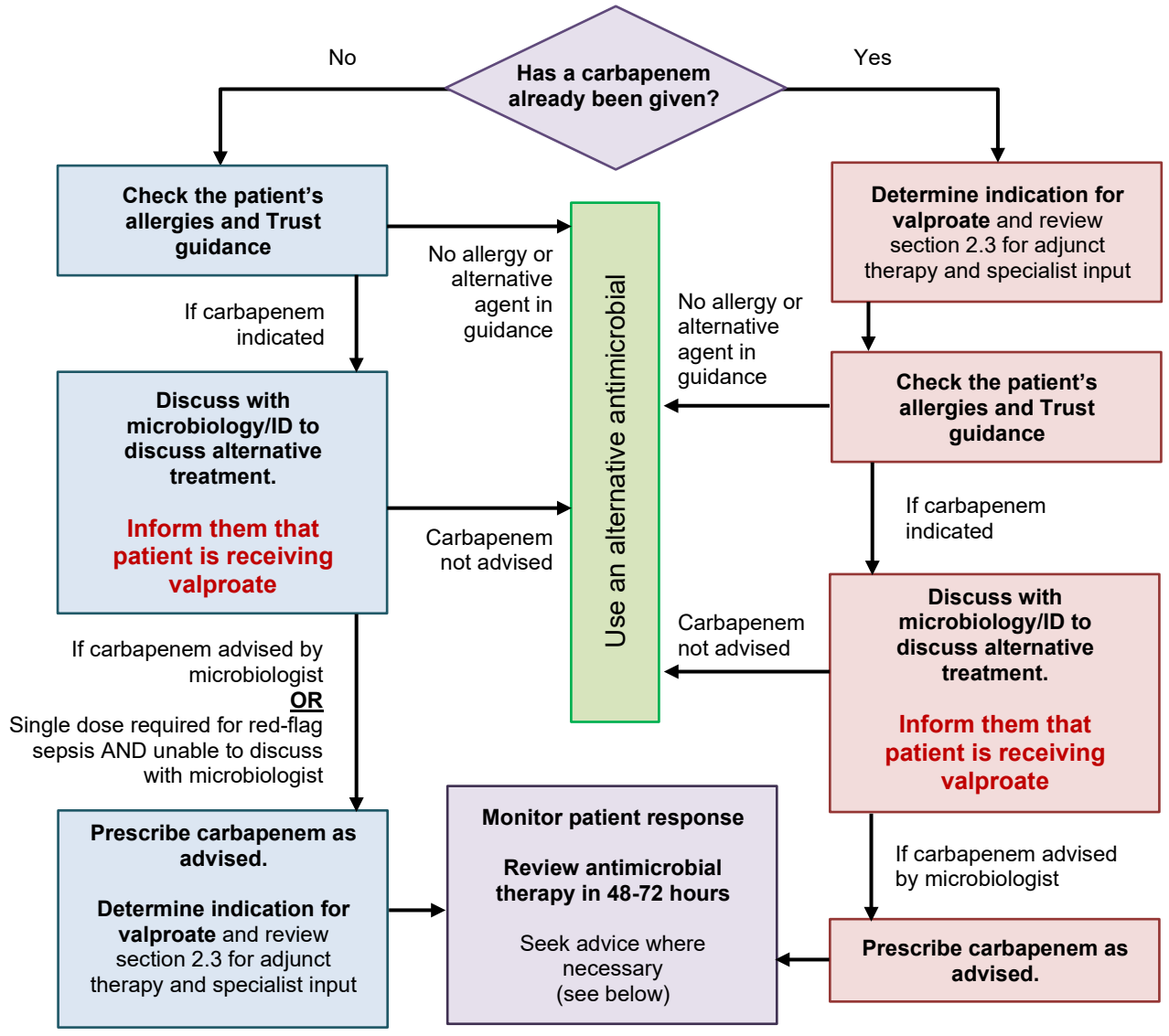
Carbapenem antibacterial agents (meropenem, ertapenem, and imipenem) cause reductions in serum valproate levels of up to 90% within 24-hours of carbapenem initiation. **This interaction is complex, persistent, and not resolved by valproate dose increases.** This guidance should be used by prescribers and pharmacists to appropriately manage patients who are taking valproate (as sodium valproate or valproic acid) but also require broad-spectrum antibacterial therapy.

## 2. Guideline Standards and Procedures

### 2.1. Investigate allergies

- If a carbapenem is indicated because the patient is thought to be allergic to penicillin this must be investigated further to clarify the adverse reaction. The allergy should be assessed and documented in line with NICE CG183 Drug allergy: diagnosis and management.
- If the patient does not have a true allergy to penicillin consider using an alternative to a carbapenem as per Trust guidelines for the specific condition (see Antimicrobial Website or App, or the Clinical Guidelines and Policies Library on Insite)

### 2.2. Follow this pathway for all patients



## 2.3. Actions to take if patient has received, or needs to receive, a carbapenem alongside valproate

**Ensure indication for valproate has been clarified with the patient and/or their medical records**

### 2.3.1. Adjunct anticonvulsant therapy for Adults taking valproate for seizure control

- Sodium valproate must not be stopped. Ensure patient's usual dosing regimen is maintained throughout adjunct therapy.
- Give 1000 mg levetiracetam as a loading dose
- Then give 500 mg levetiracetam twice-daily, commencing 12 hours after the loading dose
- Give levetiracetam throughout carbapenem treatment and continue for 14 days after carbapenem is stopped

### 2.3.2. Adjunct anticonvulsant therapy for Children taking valproate for seizure control

- Sodium valproate must not be stopped. Ensure patient's usual dosing regimen is maintained throughout adjunct therapy.
- Discuss options with paediatric neurologist to determine optimal agent
    - First-line option is usually levetiracetam – Loading dose 20 mg/kg (maximum 1000 mg) IV over 15 minutes as a loading dose. Then maintenance doses of 10mg/kg BD (max 500 mg) oral or IV every twice daily, commencing 12 hours after the loading dose.
- Give adjunct throughout carbapenem treatment and continue for 14 days after carbapenem is stopped

### 2.3.4. Managing seizures in patients receiving additional anticonvulsant therapy

- Follow Trust policies and guidelines appropriate to the clinical area for managing seizures
- These can be found on the Clinical Guidelines and Policies Library on Insite: http://bit.ly/PAGLSeizures)
- Refer patient case to neurology for further advice

### 2.3.5. Managing patients taking valproate for other indications

- Valproate may be taken for other indications such as migraine prophylaxis, or mania
- Advice should be sought from the relevant specialist if valproate is being used for an indication other than for epilepsy or seizure control
- Do not prescribe levetiracetam in these patients as it is unlikely to provide any benefit

## 2.4. Obtaining further advice

**You must inform the microbiologist that the patient is taking valproate when discussing any antimicrobial treatment.**

- Advice should be sought from microbiology/ID in the following circumstances
    - To obtain advice on alternative antimicrobials at any point during treatment
    - To obtain advice on choice of agent when undertaken and IV to Oral switch where there is no clear option in the UHL antimicrobial guidance.
    - Patient continues to have seizures in spite of additional anticonvulsant cover (note: carbapenem agents can reduce seizure threshold in their own right)

- Advice should be sought from neurology in the following circumstances
    - Patient is intolerant or allergic to levetiracetam
    - Patient is already taking levetiracetam before carbapenem initiated
    - Patient has a history of refractory epilepsy
    - Patient has a seizure whilst receiving adjunct levetiracetam for the above reasons

- To determine alternative treatment in patients that has used levetiracetam previously but was not effective.

- Advice should be sought from a clinical pharmacist in the following circumstances
  - Optimising levetiracetam regimens
  - Reviewing and optimising drug regimens for patients for whom neurology recommend alternative anticonvulsant cover.

## 3. Education and Training

Although no formal education and training is required:

- Medics working within neurology, microbiology, infectious diseases, and emergency & acute medicine must be made aware of this guideline
- All pharmacists must be made aware of this guideline
- Reference to this guideline will be made on the antimicrobial website and apps, and any relevant antimicrobial guidance and policies.

## 4. Monitoring Compliance

| What will be measured to monitor compliance | How will compliance be monitored | Monitoring Lead | Frequency | Reporting arrangements |
|---|---|---|---|---|
| Rationale for dual prescribing of carbapenem and sodium valproate | Identify patients using electronic systems (Nervecentre, ICE, JAC)<br><br>Notes review to determine rationale and if guidance was followed. | Neurology Consultants | 12 months | Neurology audit and quality meetings |
| Continuation of treatment for 14 days after carbapenem cessation | Discharge letters can be audited | Lead Pharmacist for Neurology | 12 months | Neurology audit and quality meetings |

## 5. Supporting References


- Stockley's Drug Interactions (2016) Monograph on interaction between "valproate + carbapenems", accessible via *medicinescomplete.com* [http://bit.ly/2o0CO50] accessed 06/03/2023
- UHL Antimicrobial guidance [https://viewer.microguide.global/UHL/Abx] accessed 06/03/2023
- Tobin. J. K., *et al*. (2009) Valproic acid-carbapenem interaction: report of six causes and a review of the literature, *Drug Metabolism and Drug Interactions*, **24**:153-182 [Will be of interest to those wishing to understand the proposed mechanisms of this drug-drug interaction]
- NICE (2014) Drug allergy: diagnosis and management https://www.nice.org.uk/guidance/cg183 [accessed 06/03/2023)


## 6. Key Words

Meropenem, imipenem, ertapenem, valproate, sodium valproate, valproic acid, anticonvulsant

| CONTACT AND REVIEW DETAILS | |
|---|---|
| **Guideline Lead (Name and Title)**<br>Rachel Leithead<br>Advanced Specialist Pharmacist, Antimicrobials | **Executive Lead**<br>Medical Director |
| **Antimicrobial Working Party Review**<br>Ratified:<br>Review Due: March 2026<br>Reference: AWP92 | **Policy and Guideline committee Review**<br>**28 April 2023** |

| Date | Issue Number | Reviewed By | Details of Changes made during review: |
|---|---|---|---|
| September 2017 | 1.1 | Mark Lawden – Consultant Neurologist<br><br>Deborah Modha – Consultant microbiologist<br><br>David Harris – Principal pharmacist for Women's and Children's Division<br><br>David Kearney – Lead pharmacist for ESM | No changes |
| May 2019 | 2 | Mark Lawden – Consultant Neurologist<br><br>Deborah Modha – Consultant microbiologist<br><br>David Harris – Principal pharmacist for Women's and Children's Division<br><br>David Kearney – Lead pharmacist for ESM<br><br>Ryan Hamilton – Specialist pharmacist, Antimicrobials & Acute Medicine | • Updated flow diagram regarding determining the indication for valproate as this will affect actions<br>• Management points (previously 2.3-2.6) updated into one single management section, with subsections.<br>• Subsections clarified to relate to indication for valproate. Levetiracetam specifically excluded from non-seizure scenarios. |
| March 2023 | 3 | Rachel Leithead – Advanced specialist pharmacist – antimicrobials | • Updated investigating allergy section with reference to NICE<br>• Updated electronic systems in the monitoring compliance section<br>• Updated link to antimicrobial website |