NHS Grampian

Guidance For Switching Oral Anti-Seizure Medication to Other Routes of Administration For Healthcare Professionals Working Within NHS Grampian

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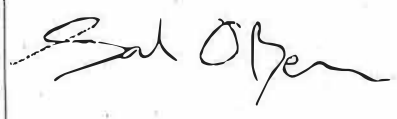		

Identifier:	Review Date:	Date Approved:
NHSG/Guide/Oral_AntiSeizMeds/MGPG1311	August 2024	August 2022

Uncontrolled when printed

Version 1

Executive Sign-Off

This document has been endorsed by the Director of Pharmacy and Medicines Management

Signature:  _____

Title:	Guidance For Switching Oral Anti-Seizure Medication to Other Routes of Administration For Healthcare Professionals Working Within NHS Grampian
Unique Identifier:	NHSG/Guide/Oral_AntiSeizMeds/MGPG1311
Replaces:	**N/A**

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Lead Author/Co-ordinator:	Lead Pharmacist, Grampian Medicines Information Centre
Subject (as per document registration categories):	Guidelines
Key word(s):	Brivaracetam, cannabidiol, carbamazepine, cenobamate, clobazam, clonazepam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, sodium valproate, stiripentol, topiramate, vigabatrin, zonisamide, epilepsy, anti-epileptic medication, anti-seizure medication, intravenous, nasogastric, rectal, route of administration, conversion, switching, therapeutic equivalency, percutaneous endoscopic gastrostomy, jejunal
Process Document: Policy, Protocol, Procedure or Guideline	Guideline
Document application:	NHS Grampian
Purpose/description:	To assist with the ongoing treatment with anti-epileptic medication when the oral route is unavailable

Responsibilities for implementation:

Organisational:	Chief Executive and Management Teams
Corporate:	Senior Managers
Departmental:	Heads of Service/Clinical Leads
Area:	Line Managers
Hospital/Interface services:	Assistant General Managers and Group Clinical Directors
Operational Management Unit:	Unit Operational Managers

Policy statement:	It is the responsibility of all staff to ensure that they are working to the most up to date and relevant policies, protocols procedures.
Review:	This policy will be reviewed in three years or sooner if current treatment recommendations change.

Responsibilities for ensuring registration of this document on the NHS Grampian Information/SharePoint: Pharmacist, Pharmacy and Medicines Directorate

Responsibilities for review of this document:	Grampian Medicines Information Centre
Responsibilities for ensuring registration of this document on the NHS Grampian SharePoint:	Pharmacy and Medicines Directorate
Physical location of the original of this document:	Pharmacy and Medicines Directorate
Job/group title of those who have control over this document:	Medicines Information Pharmacist
Responsibilities for disseminating document as per distribution list:	Medicines Information Pharmacist

Revision History:

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked* (Identify page numbers and section heading)
May 2022		New document	

* Changes marked should detail the section(s) of the document that have been amended i.e. page number and section heading.

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1 Introduction

Anti-seizure medications are considered critical medicines and doses should not be delayed or omitted[1]. Therefore, if the oral route is unavailable, other routes of administration should be considered.

Where no other routes of administration are available (due to lack of access or unavailability of a suitable formulation), and the indication is epilepsy, advice should be sought from neurology regarding management of the patient.

This document has been produced based on the most up-to-date information available. Specific factors relating to an individual patient may dictate a different approach. This document is not a substitute for professional clinical judgement. Where there are any concerns or individual patient advice is required please contact your Clinical Pharmacist, or the Grampian Medicines Information Centre on 01224 552316.

2 General information

The indication for the anti-seizure medication should be determined in all cases. Anti-seizure medicines can be used to treat other conditions.

Crushing and/or dispersing of tablets or the opening of capsules is rarely covered by the product licence and licensed routes of administration should be explored in the first instance. However, there may be no other option for some patients. Only prescribers can authorise the unlicensed use of medicines. Authorisation by the prescriber should be obtained (ideally in writing) prior to any adjustment in how an oral dosage is administered. The MHRA hierarchy should be considered while making decisions about medication, however this should not be seen as a barrier to timely and appropriate clinical care

3 Medicines and Healthcare products Regulatory Agency (MHRA)/ Commission on Human Medicines (CHM) advice: 'Antiepileptic drugs: updated advice on switching between different manufacturers' products' (November 2017)

The MHRA statement below should be considered prior to using this guidance:

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of antiepileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

1. Different antiepileptic drugs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers' products of a particular drug may cause adverse effects or loss of seizure control;

2. Antiepileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. These categories are listed below;

3. When it is necessary for a patient to be maintained on a specific manufacturer's product (e.g. when using carbamazepine for the management of epilepsy) this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder);

4. This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);

5. Report on a Yellow Card any suspected adverse reactions to antiepileptic drugs, including any adverse effect that could be attributed to a change in formulation or manufacturer;

6. Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);

7. Usual dispensing practice can be followed when a specific product is not stated, as per the MHRA statement. However, it would be best practice to confirm the indication for medications, particularly those in Category 1, prior to prescribing generically or accepting a generic prescription, due to the potential risk to the patient.

3.1 Anti-seizure medication risk-based categories

Note: medicines that have come to market since the publication of the MHRA statement will not be classified below (e.g. cenobamate, stiripentol). Therefore, clinical judgement will be required for these medications.

Category	Medications	Advice for prescribing
Category 1	Carbamazepine, phenobarbital, phenytoin, primidone	For these medications, prescribers are advised to ensure that their patient is maintained on a specific manufacturer's product.
Category 2	Clobazam, clonazepam, eslicarbazepine acetate, lamotrigine, oxcarbazepine, perampanel, rufinamide, topiramate, valproate, zonisamide	For these medications, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency, treatment history, and potential implications to the patient of having a breakthrough seizure. Non-clinical factors as for Category 3 drugs should also be considered.
Category 3	Brivaracetam, ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, vigabatrin.	For these medications, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product as therapeutic equivalence can be assumed, however, other factors are important when considering whether switching is appropriate. Differences between alternative products (e.g. product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.

For further advice, please contact Pharmacy (Clinical Pharmacist or Medicines Information within core hours, Oncall Pharmacist out-of-hours).

4 Guidance for switching anti-seizure medications from the oral route to the intravenous or rectal route

Table 1. Oral to intravenous or rectal route
IV = intravenous, N/A = not applicable (not available via these routes)

Medicine	ORAL → IV CONVERSION (total daily dose equivalence)	ORAL → IV FREQUENCY	ORAL → IV EXAMPLE	COMMENTS	ORAL → Rectal
Brivaracetam	Same dose	Same frequency	50mg twice daily oral → 50mg twice daily IV	SPC states that there is no experience of IV use >4 days – overall duration at physician's discretion	N/A
Cannabidiol (Epidyolex only)	N/A	N/A	N/A	N/A	N/A
Carbamazepine	N/A	N/A	N/A	N/A	Carbamazepine 100mg tablet or liquid is equivalent to carbamazepine 125mg suppository. If oral route unavailable, consider rectal administration. Maximum dose of 1g in four divided doses. Licensed for use for up to 7 days.
Cenobamate	N/A	N/A	N/A	N/A	N/A
Clobazam	N/A	N/A	N/A	N/A	N/A

Medicine	ORAL → IV CONVERSION (total daily dose equivalence)	ORAL → IV FREQUENCY	ORAL → IV EXAMPLE	COMMENTS	ORAL → Rectal
Clonazepam	N/A	N/A	N/A	N/A	N/A
Ethosuximide	N/A	N/A	N/A	N/A	N/A
Gabapentin	N/A	N/A	N/A	N/A	N/A
Lacosamide	Same dose	Same frequency	100mg twice daily oral → 100mg twice daily IV	There is experience of IV use for up to 5 days, but overall use is at physician's discretion	N/A
Lamotrigine	N/A	N/A	N/A	N/A	N/A
Levetiracetam	Same dose	Same frequency	500mg twice daily oral → 500mg twice daily IV	N/A	N/A
Oxcarbazepine	N/A	N/A	N/A	N/A	N/A
Perampanel	N/A	N/A	N/A	N/A	N/A
Phenobarbital	Same dose	Same frequency	100mg at night oral → 100mg at night IV	*Almost* bioequivalent. IV route gives a marginal dose increase - monitor response	N/A

Medicine	ORAL → IV CONVERSION (total daily dose equivalence)	ORAL → IV FREQUENCY	ORAL → IV EXAMPLE	COMMENTS	ORAL → Rectal
Phenytoin Capsules	Same dose	Increase (3-4 times daily)	300mg once daily oral → 100mg three times daily IV	Therapeutic drug monitoring required. Consider taking pre-dose trough level before re-dosing. Steady state achieved after 5-7 days. Monitor ECG & BP	N/A
Phenytoin Liquid	90:100	Increase (3-4 times daily)	270mg once daily oral → 100mg three times daily IV	Therapeutic drug monitoring required. Consider taking pre-dose trough level before re-dosing. Steady state achieved after 5-7 days. Monitor ECG & BP	N/A
Pregabalin	N/A	N/A	N/A	N/A	N/A
Primidone	N/A	N/A	N/A	N/A	N/A
Rufinamide	N/A	N/A	N/A	N/A	N/A

Medicine	ORAL → IV CONVERSION (total daily dose equivalence)	ORAL → IV FREQUENCY	ORAL → IV EXAMPLE	COMMENTS	ORAL → Rectal
Sodium valproate EC/Liquid	Same dose	Same frequency	500mg three times daily oral → 500mg three times daily IV	N/A	N/A
Sodium valproate M/R (Chrono)	Same dose	Increase (3 times daily)	750mg morning and night oral → 500mg three times daily	N/A	N/A
Stiripentol	N/A	N/A	N/A	N/A	N/A
Topiramate	N/A	N/A	N/A	N/A	N/A
Vigabatrin	N/A	N/A	N/A	N/A	Seek specialist advice. Has been administered rectally in children using granules. Given at the same dose as oral administration. Sachets are dissolved in a small amount of water prior to administration. Granules are not licensed for rectal use.
Zonisamide	N/A	N/A	N/A	N/A	N/A

5 Guidance for switching anti-seizure medications from the oral route to NG, PEG or jejunal administration

Tubes may terminate in the stomach or the jejunum, and they may enter via the nose or through the abdominal wall. It is usually possible to give medicines via these enteral tubes, but it can be difficult to find guidance on the best approach. Important considerations include the diameter of the tube (and therefore risk of blockage), the suitability of the formulation used, whether the stability of the medication might be affected by the acid environment of the stomach, or whether absorption might be affected by bypassing the stomach in the case of jejunal tubes.

General recommendations for drug administration via enteral tubes:

- Use enteral syringes at all times, not injection syringes.
- For tubes terminating in the stomach, tap water is acceptable. For tubes terminating in the jejunum, sterile water should be used.
- Stop feed and/or flush enteral tube with 15-30mL of water prior to drug administration.
- Ensure the patient is sitting up at an angle of at least 30 degrees to avoid reflux of medication or water.
- Give medication via enteral tube as directed by the guidance within the table.
- If more than one medicine is being administered, flush with at least 10mL of water between each medication.
- After administration of the last medication, flush tube well with 15-30mL of water after the dose.
- Restart feed if a prolonged break in feed is not advised.

Practical advice for patient/carer/healthcare professional administering medicines:

- Do not crush modified release preparations. These might be indicated by ‘MR’, ‘SR’ or ‘XL’ after the brand name. Additionally, do not crush enteric coated medicines. Some dispersible tablets are unsuitable for crushing. If you are unsure, check with Pharmacy.
- Ensure protective equipment such as gloves and masks are worn when crushing tablets.

If a tablet can be dispersed, this would ideally be carried out in a closed system, such as the barrel of an enteral syringe. To do this, remove the plunger and place the tablet in the barrel of a 50mL enteral syringe. Replace the plunger and draw up 10-15mL of water. Cap the syringe and allow the tablet to disperse, agitating if necessary. Shake well, remove the cap and administer the dose via the feeding tube. Flush with water as usual, and dispose of the syringe.

Table 2. Oral to enteral route
NG = nasogastric, PEG = percutaneous endoscopic gastrostomy

Medicine	Form	Instructions	Feed Directions	Additional Information
Brivaracetam	Oral Solution	Solution can be given undiluted, but may be diluted with an equal volume of water if required.	A prolonged break in feeding is not required before/after administration.	The solution is licensed for NG and PEG administration. If administered via jejunal tube, monitor for loss of efficacy or increased side effects.
Cannabidiol (Epidyolex only)	Oral solution	Solution can be given undiluted.	A prolonged break in feeding is not required before/after administration, but give in a consistent manner	If administered via jejunal tube, monitor for loss of efficacy or increased side effects

Medicine	Form	Instructions	Feed Directions	Additional Information
Carbamazepine	Liquid	Dilute with an equal volume of water.	A prolonged break in feeding is not required before/after administration, but give in a consistent manner. An alteration in carbamazepine absorption should be considered in any patient who commences or discontinues enteral feeds. Drug level monitoring should be carried out as necessary.	400mg modified release (MR) twice daily is equivalent to 200mg liquid four times daily. If administered via jejunal tube, monitor for loss of efficacy or increased side effects.
Cenobamate	Tablets	No information. Discuss with Pharmacy.		
Clobazam	Tablets	The tablets can be dispersed in water for administration. They disperse in one to five minutes. Take care to ensure the whole dose is administered.	A prolonged break in feeding is not required before/after administration.	If administered via jejunal tube, monitor for loss of efficacy or increased side effects.

Clonazepam	Oral Solution	Use an oral solution licensed for administration via enteral feeding tubes (non-PVC tubes only). Flush well with three separate flushes of 5mL water, as the solution is oily.	A prolonged break in feeding is not required before/after administration.	If administered via jejunal tube, monitor for loss of efficacy or increased side effects.
	Tablets	The tablets can be dispersed in at least 30mL of water (volume required to prevent binding to the tube) for administration. They disperse in less than two minutes.		
Ethosuximide	Syrup	Syrup can be diluted with water immediately before administration if necessary to reduce viscosity.	A prolonged break in feeding is not required.	If administered via jejunal tube, monitor for loss of efficacy or increased side effects.

Medicine	Form	Instructions	Feed Directions	Additional Information
Gabapentin	Oral solution	Give undiluted	A prolonged break in feeding is not required before/after administration.	The Rosemont and Colonis liquids are licensed for NG or PEG administration and should be used if available. If administered via jejunal tube, use the capsules and monitor for loss of efficacy or increased side effects.
	Capsules	Dissolve contents in water and give immediately.		
Lacosamide	Syrup	Syrup can be diluted with water immediately before administration if necessary to reduce viscosity.	A prolonged break in feeding is not required before/after administration.	If administered intrajejunally, monitor for loss of efficacy or increased side effects.
Lamotrigine	Dispersible Tablets	Disperse in 10-15mL of water immediately prior to administration.	A prolonged break in feeding is not required before/after administration.	Monitor closely for changes in efficacy or increased side effects. If administered intrajejunally, monitor for loss of efficacy or increased side effects.

Medicine	Form	Instructions	Feed Directions	Additional Information
Levetiracetam	Granules	Suspend the granules by shaking in at least 10mL of water for at least 2 minutes. After the dose, flush twice with 10mL of water each time.	A prolonged break in feeding is not required before/after administration.	The granules (Desitrend) are licensed for tube administration and should be used if available. Can also be administered intrajejunally. Monitor closely for changes in efficacy or increased side effects.
	Oral solution	Solution can be given undiluted.		
	Tablets	Crush and disperse with water		
Oxcarbazepine	Oral Suspension	The suspension can be diluted with water to aid administration.	A prolonged break in feeding is not required before/after administration.	If administered intrajejunally, monitor for loss of efficacy or increased side effects.
Perampanel		No information. Discuss with pharmacy.		

Medicine	Form	Instructions	Feed Directions	Additional Information
Phenobarbital	Elixir	Elixir can be given undiluted.	A prolonged break in feeding is not required before/after administration.	The elixir contains 38% alcohol. If administering via jejunal tube, consider diluting the liquid formulation to reduce osmolarity.
	Tablets	The tablets may be crushed and mixed with 15-30mL of water for administration.		

Medicine	Form	Instructions	Feed Directions	Additional Information
Phenytoin	Oral Suspension (Phenytoin base)	Shake well and mix with an equal volume of water.	Withhold feeds for 2 hours before and 2 hours after each dose.	Flush with 30-60mL of water. Patient response and levels should be monitored carefully, specially after any changes in the feeding regimen, as the dosage may require adjustment. When converting between capsules and suspension, a dose conversion is required. 100mg phenytoin sodium (capsules) = 90mg phenytoin base (suspension). Absorption is poor intrajejunally. Monitor patient and plasma levels closely and dilute suspension to avoid GI adverse effects.
	Capsules (Phenytoin sodium)	Open and disperse the powder in 10mL of water. Leave for 5 minutes and stir to form a fine dispersion.		

Medicine	Form	Instructions	Feed Directions	Additional Information
Pregabalin	Oral Suspension	Can be given undiluted.	A prolonged break in feeding is not required before/after administration.	Flush well. Can also be administered via jejunal tube. Monitor for increased GI adverse effects
	Capsules	Open and disperse contents in 15-30mL of water.		
Primidone	Tablets	The tablets can be crushed and dispersed in 15-30mL of water for administration. The drug is poorly soluble so flush tube thoroughly.	A prolonged break in feeding is not required before/after administration.	If administered intrajejunally, monitor for loss of efficacy or increased side effects.
Rufinamide	Oral Suspension	Suspension can be given undiluted.	A prolonged break in feeding is not required before/after administration.	Suspension is licensed for administration via enteral feeding tubes. Rufinamide should be taken with food. If administered intrajejunally, monitor for loss of efficacy or increased side effects.

Medicine	Form	Instructions	Feed Directions	Additional Information
Sodium valproate	Oral Liquid	Dilute with an equal volume of water immediately prior to administration.	A prolonged break in feeding is not required before/after administration.	Do NOT crush modified release products. If converting from modified release preparations, give the same total daily dose, but divided into more frequent doses. If administered via jejunal tube, use dispersed tablets or dilute the liquid 3-4 times with water. Monitor for loss of efficacy or increased side effects.
	Epilim Crushable Tablets	Crush and disperse in 10mL of water.		
Stiripentol		No information. Discuss with pharmacy.		

Medicine	Form	Instructions	Feed Directions	Additional Information
Topiramate	Tablets	The tablets can be crushed and dispersed in 15-30mL of water for administration.	A prolonged break in feeding is not required before/after administration.	It is not recommended to open capsules and sprinkle the contents into water as the beads readily stick to tubing causing blockage. If administered intrajejunally, monitor for loss of efficacy or increased side effects.
Vigabatrin	Soluble Tablets	Dissolve in 5-10mL if water for administration.	A prolonged break in feeding is not required before/after administration.	The soluble tablets are not licensed for use in adults. The sachets have been administered in a much smaller volume (10mL) without blockage.
	Sachets	Dissolve the sachet in 100mL water for administration.		
	Tablets	The tablets can be crushed and dispersed in water for administration.		

Medicine	Form	Instructions	Feed Directions	Additional Information
Zonisamide	Oral Suspension	Shake well before use. The suspension can be given undiluted, or diluted with an equal volume of water. The tube must be flushed three times with 5mL of water after each dose.	A prolonged break in feeding is not required before/after administration.	There is no information on jejunal administration. If administered intrajejunally, monitor for loss of efficacy or increased side effects.
	Capsules	The capsules can be opened and the contents dispersed in water or apple juice for administration.		

6 Consultation list

Dr Graham Mackay	Consultant Neurologist
Karen McKessack	Clinical Pharmacist – Medical Team Lead
Askal Forbes	ANP
Rebecca Anderson	Senior Medicines Information Pharmacist
Morag Smart	Neurology Pharmacist
Julie Le Gourrierec	Rotational Pharmacist/On call Pharmacist

Contributors

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7 References

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3 BNF accessed online via Medicines Complete

4 NEWT guidelines

5 eMC – individual monographs

6 Handbook of Drug Administration via Enteral Feeding Tubes

7 NHS Grampian Guideline For The Administration Of Medicines To Adults Via Enteral Feeding Tubes