Epilepsy Subcommittee Report

November 2024 – March 2025

Background

The Epilepsy Subcommittee was constituted following the receipt of numerous external comments on the draft epilepsy sections of the Primary Healthcare (PHC) and Adult Hospital level (AHL) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). Comments were received regarding the terminology and classification of epilepsy; specific pharmacological agents; management according to seizure type; special population groups; status epilepticus, and rehabilitation

Additionally, due to the concerns regarding valproate use in pregnancy and women and men of child-bearing potential, NEMLC was concerned with the Paediatric Hospital recommendation of valproate as first line treatment for generalised tonic-clonic seizures, absence seizures, and children with HIV.

Key issues arising from external comments and NEMLC discussion included:

- Alignment between levels of care regarding terminology and classification as well as treatment choices was necessary.
- Sentence level changes related to description, general measures, medicine treatment and referral criteria were required.
- Treatment algorithms were not broadly acceptable. While editing and formatting was necessary, medicine recommendations were queried and the need for and/or treatment options was raised.
- Valproate use in children would very likely be continued in girls and women of child-bearing potential and making it a first-line recommendation encourages its use. Experience reported from the Western Cape was that active engagement with PTCs and family physicians did not reduce valproate prescriptions or strengthen use of acknowledgement of risk forms.
- The long titration period required for lamotrigine makes it unacceptable to some stakeholders as first-line treatment in all paediatric and adult epilepsies.
- There is a demand for increased access to levetiracetam, including at PHC level.

The purpose, functions and decision-making process of the Epilepsy Subcommittee detailed in the Epilepsy Subcommittee terms of reference are as follows:

1. The purpose of the Epilepsy Subcommittee was to align the STGs on epilepsy across all levels of care (i.e. primary, secondary, and tertiary/quaternary care) and age groups (i.e. children, adolescents and adults) to ensure a continuum of care, using the medicines currently on the EML, and to identify gaps in EML treatment.

2. The functions of the Epilepsy Subcommittee included, but were not limited to, the following:
    - Assessing the current epilepsy STGs across all levels of care including EML items indicated for paediatric and adult male and female patients, classification of seizures, and guidance for acute versus maintenance treatment.
    - Preparing recommendations for updating of epilepsy chapters of the STGs, across all levels of care by end of March 2025; and
    - Assisting with the review of bid specifications for national tenders as needed.

Aim of this report

The aim of this report is to summarise the work conducted to date by the Epilepsy Subcommittee. Key changes to the STGs and the rationale for those changes are presented. Gaps in treatment requiring further consideration are discussed with suggested ways forward.

Methods

Members were appointed to the Subcommittee by the Chief Director: Sector Wide Procurement in the Affordable Medicines Directorate of the National Department of Health. The Subcommittee was comprised of NEMLC members, experts who had served on either the PHC and Adult Hospital or the Paediatric Hospital Expert Review Committees, external clinical experts, and a secretariat. For the external clinical experts, invitations to serve on the Subcommittee were first sent to those who had submitted comments on the epilepsy STGs. Thereafter, individual experts were invited upon recommendation by a member of the Subcommittee and according to their discipline to ensure adequate representation of relevant expertise. The Subcommittee members were as follows:

Epilepsy Subcommittee:

Adj. Prof L Robertson (Chairperson)	Psychiatrist: Sedibeng District Health Services & Department of Psychiatry, University of the Witwatersrand
Dr A Gray (Vice-Chair)	Pharmacist: Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal.
A/Prof K Cohen	Pharmacologist: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
A/Prof T Crowley	Professional Nurse: School of Nursing, University of Western Cape
Dr MV Gule	Neurologist, Groote Schuur Hospital & University of Cape Town
Ms S McGee	Insight Actuaries and Consultants
A/Prof U Mehta	Pharmacist and Pharmacovigilance Consultant: University of Cape Town
Dr J Mohale	Family Physician: Chris Hani Health District & Walter Sisulu University
Dr G Reubenson	Paediatrician: Rahima Moosa Mother and Child Hospital & Department of Paediatrics, University of the Witwatersrand
Dr S Rossouw (resigned)	Neurologist: Livingstone Hospital, Eastern Cape
Dr T Ruder	Paediatrician: Division of Community Paediatrics, School of Public Health, University of Witwatersrand
Dr J Taylor	Pharmacology Registrar: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
Prof J Wilmshurst	Paediatric Neurologist: Head of Paediatric Neurology, Red Cross War Memorial Children's Hospital

Secretariate

Dr J Riddin	National Department of Health, Essential Drugs Programme
Ms K MacQuilkan	Health System Research Unit, SAMRC
Dr M Reddy	Health System Research Unit, SAMRC

Revision of the STGs

In revising the STGs, consensus-based decision making was used. Matters where the Subcommittee were unable to reach consensus were discussed with NEMLC on 27 February 2025.

The International League Against Epilepsy (ILAE) classification system,[1] which has been incorporated into the WHO ICD-11 nomenclature,[2] was used to reorganise the guidance. The STGs for each level of care were collapsed into one document so that guidance could be written for a continuum of care according to diagnosis.

The NICE 2022 Guideline (updated in January 2025) *Epilepsies in children, young people and adults*[3] and its evidence reviews were used to inform changes to the indications and hierarchy of choice of the antiseizure medicines (ASMs) already on the EML. An AGREE II (Appraisal of Guidelines, for Research, and Evaluation) assessment of the NICE Guideline was conducted in duplicate to evaluate the process of guideline development and quality of reporting using the AGREE II assessment tool. The NICE Guideline was rated as a high-quality clinical practice guideline with AGREE II scores of 97% overall and 98% for rigour of development (as presented in Appendix A). As the NICE evidence reviews are of high quality, alternative guidelines were not sourced. Additionally, although NEMLC acknowledged the difference in resource settings between counties NEMLC did not recommend a GRADE-ADOLOPMENT of the NICE 2022 guideline at this time.

In addition to redrafting of the guidance, a tender-related query arose regarding carbamazepine immediate versus controlled release. The question was whether to continue to tender for both preparations or only for the immediate or the controlled release preparation. A rapid review of evidence was therefore conducted (Appendix B) and discussed below.

Results

After collating and comparing the STGs for each level of care, acute management of epileptic seizures and management of febrile seizures were separated from maintenance treatment of epilepsy, so that the range of conditions were spread across four sections:

1. Epileptic Seizures; (PHC, AHL and Paediatric Hospital Level)
2. Status Epilepticus; (PHC, AHL and Paediatric Hospital Level)
3. Febrile Seizures; (PHC and Paediatric Hospital Level)
4. Epilepsy; (PHC, AHL and Paediatric Hospital Level)

Epileptic Seizures and Status Epilepticus

Previous STGs

The 2019 AHL, 2020 PHC level and 2023 Paediatric Hospital Level STGs differed as follows:
PHC: Differential diagnosis and important causes of seizures that must be excluded listed in the description. Seizure types described briefly under epilepsy section of CNS chapter. Medicine treatment for convulsive status epilepticus (i.e., status epilepticus with generalised tonic-clonic (GTC) seizures) was located separately in Chapter 21 Emergencies and Injuries. No timing of status and no supportive interventions were provided and there was no second level intervention for adults. Post-seizure recommendations in CNS chapter included the need to investigate the cause and evaluate for possible epilepsy.
Paediatric Hospital: Seizures, febrile seizures, and status epilepticus presented in separate sections prior to section on epilepsy. Aetiological and clinical classification of seizures were

[1] International League Against Epilepsy. EpilepsyDiagnosis.org. 30 June 2024. Available at https://www.epilepsydiagnosis.org/
[2] World Health Organization. ICD-11 for Mortality and Morbidity Statistics. Available at: https://icd.who.int/browse/2025-01/mms/en#1397288146
[3] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

described using ILAE terminology.[4] Emphasis was placed on identifying cause of seizure. Guidance on laboratory and neuro-imaging investigations provided. For convulsive status epilepticus, medicine treatment and supportive interventions were provided using ILAE approach of early, established and refractory status, although timing was not 100% accurate.

Adult Hospital: Acute management of seizures was briefly noted in the epilepsy section. No differential diagnosis, or description of differing seizure types or aetiologies. Convulsive status epilepticus followed the section on epilepsy, with exclusion of some possible causes of status epilepticus noted under general measures and a post-seizure recommendation to commence phenytoin. Implication from the section was that seizures and convulsive status epilepticus are always part of epilepsy.

Table 1. Medicine treatment for status epilepticus at each level of care – previous guidance

PHC – Children	Paediatric Hospital (2023)	PHC – Adults (2019)	Adult Hospital (2020)
Initial treatment Midazolam, buccal or IM, or Diazepam, rectal Repeat benzodiazepine if no response after 10 minutes	0-5 mins Lorazepam, IV or IM or Diazepam, rectal or Midazolam, buccal	Initial treatment Midazolam, IM or buccal Or Diazepam, IV Repeat once after 5 – 10 mins if still fitting	Initial treatment Lorazepam, IV or Midazolam, IV, IM or buccal, or Clonazepam, IV or Diazepam, IV Repeat once after 5 – 10 mins if necessary Simultaneously, administer Phenytoin, IV infusion
No response to two doses benzodiazepines and convulsions lasting > 20 mins: Phenobarbital tablets, crushed via NGT	5 – 30 mins Repeat benzodiazepine, add Phenytoin, IV or Phenobarbital, IV If no response after 15 - 20 mins, repeat dose of phenytoin or phenobarbital (use alternative to what was used above)	No guidance	If further/continued seizures Repeat phenytoin infusion at half the dose.
No guidance - refer	30-60 mins Refer ICU Consider midazolam infusion, intubation and ventilation	No guidance - refer	Seizures continuing >30mins Propofol infusion or Midazolam infusion

Blue = PHC level; Orange = Paediatric Hospital level; Green = Adult Hospital

The revised STGs**,** took into consideration guidance from all three levels of care and the ILAE. Of note, the revised STG:

- provides a generic description of epileptic seizures, differential diagnoses, and important causes to exclude.
- briefly describes different seizure types with link to ILAE website
- separates management into a) children < 13 years of age and b) adolescents and adults. The rationale for this separation is that acute causes of epileptic seizures and medicine doses in adolescents are like those of adults and inpatient care of adolescents is in adult wards. Special considerations for each age group are listed under the respective section.
- separates treatment of convulsive status epilepticus using ILAE time points of 5 minutes (t_1 abnormally prolonged seizure) and 30 minutes (t_2 when a seizure may cause long-term consequences) and level 1, 2 and 3 interventions. The existing Paediatric Hospital table has been expanded to include simultaneous supportive interventions.
- post-seizure guidance is provided to include the post-ictal phase and active follow-up period.

[4] International League Against Epilepsy. Epilepsy Classification. 30 June 2024. Available at: https://www.epilepsydiagnosis.org/epilepsy/epilepsy-classification-groupoverview.html

- has refined the medicine treatments from the previous STGs only to clarify dosing and to expand vascular access in children to include the intraosseous route.

Updated medicine treatments for children < 13 years and for adolescents and adults are presented in tables 2 and 3.

Table 2. MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN CHILDREN < 13 YEARS (Extracted from Paediatric Hospital Standard Treatment Guidelines)

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS **5-10 minutes after seizure onset**	**LEVEL 1 INTERVENTION:** (benzodiazepines, up to 2 doses) If vascular access is available: ▪ Lorazepam, IV or IO, 0.1 mg/kg over 60 seconds (max 4 mg/dose). **OR** ▪ Midazolam, IV or IO, 0.25 mg/kg over 60 seconds, (max 10 mg/dose). **OR** ▪ Diazepam, IV or IO, 0.25 mg/kg IV over 60 seconds (max 10 mg/dose). If vascular access is not available: ▪ Lorazepam, IM or buccal, 0.1 mg/kg (max 4 mg/dose). **OR** ▪ Midazolam, IM, 0.1 mg/kg, or buccal*, 0.5 mg/kg. **OR** ▪ Diazepam, rectal**, 0.5 mg/kg (max 10 mg/dose). Expect a response within 1–5 minutes. **If the seizure does not resolve within 5 minutes after first dose, give a repeat dose of benzodiazepine.** **CAUTION** Benzodiazepines can cause respiratory depression. Monitor oxygen saturation and respiratory rate. If respiratory depression occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high care setting.	» Aim for seizure control within 30 minutes of onset. » Provide supplemental oxygen, maintain $SaO_2 \geq 95\%$. » Monitor cerebral perfusion pressure (CPP), heart rate, oxygen saturation. » Check glucose. If low, correct and start maintenance IV fluid with dextrose 5% in sodium chloride 0.9%. Do not overhydrate. » Blood gas analysis for electrolytes. Correct as required. Other biochemical disorders: Correct abnormalities, if present, e.g. glucose, calcium and sodium. Take blood for electrolytes, LFTs, FBC. If patient is a known epileptic, check therapeutic levels of antiseizure medications (ASM). If meningitis cannot be excluded, give: ▪ Ceftriaxone, IM or IV, 100mg/kg/dose stat
ESTABLISHED STATUS **10-30 minutes after seizure onset**	**LEVEL 2 INTERVENTION:** If vascular access is not available: ▪ Phenobarbital, IM 20 mg/kg. ○ Slow IM injection **OR** if no IM formulation available: ▪ Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose (Maximum dose: 4500 mg). **OR** ▪ Phenobarbital, oral, crushed and given by nasogastric tube, 20 mg/kg as a single dose. Note: Avoid repeating oral phenobarbital as it may take over an hour to achieve therapeutic concentrations, and repeat doses increase the risk of respiratory depression. If no response to phenobarbital IM or oral after 5-20 minutes, levetiracetam oral may be given via nasogastric tube. If vascular access is available: ▪ Phenytoin, IV or IO, 20 mg/kg *(diluted in sodium chloride 0.9% and infused over 20 minutes, not exceeding 3 mg/kg/min with cardiac monitoring)*. **OR** ▪ Phenobarbital, IV or IO, 20 mg/kg over 5 mins (max 600 mg/dose). **CAUTION** Do not use phenytoin to manage drug- or toxin-induced seizures. Cardiac monitoring is mandatory to ensure safe use. If phenytoin given and no response after 15–20 mins of infusion: ▪ Phenobarbital, IV or IO, 20 mg/kg over 5 mins (max 600 mg per dose).	» Consult with higher level care and refer urgently. » Prepare for intubation and ventilation. » Ensure that phenytoin is administered independently of other IV fluid, i.e. use a separate IV line, or stop maintenance fluids, flush the line with saline and commence the phenytoin infusion. » Seizures due to poisoning should **NOT** be treated with phenytoin.

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
	<u>If phenobarbital given and no response 5 mins after administration:</u> ▪ Phenytoin, IV or IO, 20 mg/kg *(diluted in sodium chloride 0.9% and infused over 20 minutes, not exceeding 3 mg/kg/min with cardiac monitoring)*. **OR** Repeat phenobarbital, IV in half doses: ▪ Phenobarbital, IV or IO, 10 mg/kg over 5 mins (max 600 mg/dose). <u>If still no response:</u> ▪ Phenobarbital, IV or IO, 10 mg/kg over 5 mins (max 600 mg/dose). Prepare for intubation if sufficiently skilled in the procedure and relevant rescue devices are available. **Refer to ICU**	
REFRACTORY STATUS Seizures persist despite treatment with adequate doses of two or three antiseizure medications **USUALLY by 30- 60 minutes after seizure onset**	**Failure of level 1 and level 2 interventions to control seizures** **Refer to ICU** Consider: » Midazolam infusion. » Maintain SaO2 ≥ 95%: Oxygen, by facemask or nasal cannulae while convulsing. » Endotracheal intubation with neuroprotective ventilation strategy (See Section 23.1: Rapid sequence intubation). » If it is necessary to ventilate, maintain PaCO2 in the low-normal range, i.e. 4.0–4.5 kPa. » Measure antiseizure medication blood concentrations if there are breakthrough seizures on medication, signs of toxicity, drug interactions or concerns about adherence.	» Stop seizure. » Support haemodynamic status. » Admit to high- or intensive-care, if possible. » Monitor: > heart rate, respiratory rate, > blood pressure, SaO2; > blood gas analysis, acid-base status; > electrolytes, blood glucose, neurological status; > fluid balance, osmolality; > Blood levels of ASM. » Cardiovascular and/or respiratory support if the patient is unable to maintain blood gases and blood pressure within the normal physiological range. **Cerebral oedema** Treat when clinically proven. See Section 13.12: Raised intracranial pressure.

<u>Note:</u>
» Watch for complications of the prolonged seizure.
» Check all possible underlining conditions.
» Watch for adverse effects of administered ASM.

* Midazolam, buccal, 0.5 mg/kg/dose. See Primary Health Care STGs and EML, Chapter 23: Standard paediatric dosing tables.
o Use midazolam for injection 5 mg in 1 mL undiluted.
o Draw up the required volume in a 5 mL syringe.
o Remove needle then administer midazolam into the buccal cavity (between gum and cheeks).
o Note: Buccal midazolam should not be used in infants < 6 months of age.

**Diazepam, rectal, 0.5 mg/kg/dose as a single dose. See Primary Health Care STGs and EML, Chapter 23: Standard paediatric dosing tables.
o Use diazepam for injection 10 mg in 2 mL undiluted.
o Draw up the required volume in a 2 mL syringe.
o Remove needle then connect syringe to an NGT and gently insert into the rectum (or insert the whole barrel of the lubricated syringe if no NGT available) and inject the contents.
o Remove NGT / syringe and hold buttocks together to minimise leakage.

Table 3: MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN ADOLESCENTS AND ADULTS (Extracted from Adult Hospital Standard Treatment Guidelines)

PHASE	MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS (5 – 10 minutes)	**LEVEL 1 INTERVENTION:** (Benzodiazepines) If IV access: ▪ Lorazepam, IV, 4 mg, administered not faster than 2 mg/minute. **OR** ▪ Midazolam, IV, 10 mg. **OR** ▪ Diazepam, IV, 10 mg administered over at least 5 minutes (not faster than 2mg/min). **OR** ▪ Clonazepam, IV, 1 mg. If no IV access: ▪ Midazolam, 10 mg, IM or buccal, using the parenteral formulation, while continuing to establish IV access If no IV access and no midazolam is available: ▪ Clonazepam, IM, 1 mg. **OR** ▪ Diazepam, rectal, 0.2 – 0.5 mg/kg as a single dose (maximum 20 mg/dose). If the seizure does not resolve 5 minutes after first dose of benzodiazepine, repeat the dose of benzodiazepine. If seizure aborts after 1 or 2 doses of benzodiazepines, but patient is at high risk of recurrent seizures (e.g., known with epilepsy and defaulted treatment), load with antiseizure medicine. **CAUTION** Benzodiazepines can cause respiratory depression. Monitor closely for respiratory depression. If this occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high-care setting.	» Stabilize and support airway breathing and circulation » Identify and treat the underlying cause of seizures such as: – Hypoglycaemia – Electrolyte derangements (e.g. calcium, sodium, potassium, magnesium and urea) – Poisoning – Intoxication/overdose (e.g. isoniazid, theophylline, tricyclic antidepressants, cocaine, methamphetamine) – Withdrawal syndromes (e.g. alcohol, benzodiazepines) » If patient is known with epilepsy and on treatment take blood for measurement of ASM levels.
ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes)	**LEVEL 2 INTERVENTION:** (Antiseizure medicine) If IV access **and not suspected to be drug- or toxin-induced**: • Phenytoin, IV, 20 mg/kg diluted in 200 ml sodium chloride 0.9% **(not dextrose containing fluid)** administered not faster than 50mg/minute (usually 20–30 minutes) with cardiac monitoring. ○ If arrhythmias/hypotension occur, interrupt infusion temporarily and reintroduce at a slower rate. **CAUTION** Do not use phenytoin to manage suspected drug- or toxin-induced seizures. Cardiac monitoring is mandatory to ensure safe use. **Note:** » **Do not use phenytoin if seizures are suspected to be drug- or toxin-induced.** To manage, proceed to level 3 intervention, refractory status epilepticus, and address the acute poisoning (See Chapter 19: Poisoning). » If phenytoin toxicity is suspected (e.g. in a patient on chronic phenytoin treatment), proceed to level 3 intervention, refractory status epilepticus. If no IV access, consider: » Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose. (Maximum dose: 4500 mg).	» Prepare for intubation/ventilation » Arrange referral to higher level of care
REFRACTORY STATUS (30 – 60 minutes)	▪ Propofol, IV, 1–2 mg/kg/dose as a bolus, followed by a continuous infusion at 1.2 mg/kg/hour. If necessary, titrate to effect by increasing infusion rate by 0.3 to 0.6 mg/kg/hour every 5 minutes (maximum rate of 12 mg/kg/hour or maximum total dose of 4 mg/kg/hour over 48 hours). **OR**	» Admit to high- or intensive-care unit, if possible. » Employ a neuroprotective ventilation strategy (See Chapter 23: Adult Critical Care)

	▪ Midazolam, IV, 0.1 – 0.2 mg/kg bolus, followed by 0.05 – 0.5 mg/kg/hour infusion, titrated to effect. **Note:** » To prevent recurrent seizures if epilepsy is diagnosed or suspected, continue treatment with the most appropriate antiseizure medication during the infusion and weaning of propofol or midazolam. » Continue propofol or midazolam infusion for 12−24 hours after the last clinical or electrographic seizure, then wean the infusion.	– If it is necessary to ventilate, maintain PaCO2 in the low-normal range, i.e. 4.0–4.5 kPa. » Monitor: – heart rate, acid-base status, – respiratory rate, blood gas analysis, – blood pressure, SaO2, – electrolytes, neurological status, – blood glucose, fluid balance, – antiseizure medication blood concentrations, osmolality.

Key changes to the medicine treatment guidance are:

- Removal of a repeat dose of phenytoin IV for all age groups. The safety of a second dose of phenytoin had previously been questioned by NEMLC but not appraised. While its safety was also raised by the subcommittee, a second dose of phenytoin (which is infused over 20 minutes) is not possible before reaching t_2 (30 minutes).
- Repeat doses of phenobarbital IV in children < 13 years to be administered in two half doses, to prevent administering too high a dose and causing respiratory depression.
- Recommendation to give ASM (phenytoin, IV) simultaneously with benzodiazepines as 1st line intervention in the Adult STGs changed to a recommendation to sequential administration.
- Replacement of recommendation to initiate phenytoin 300mg (oral) per day in adults once the seizure has resolved with a more general statement of "To prevent recurrent seizures if epilepsy is diagnosed or suspected, continue treatment with the most appropriate antiseizure medication during the infusion and weaning of propofol or midazolam." Post-seizure guidance then emphasises the need to wean ASMs unless a diagnosis of epilepsy is confirmed.
- Addition of levetiracetam administration via NGT (See appendix C).
- Addition of phenobarbital IM at PHC level (if product is available).

Identified gaps

Serious gaps in the treatment of status epilepticus exist for both children < 13 years of age and people ≥13 years, especially at PHC level of care, as follows:

<u>Access to Schedule 5 medicines</u>

- PHC Nurses and Clinical Associates are currently not authorised to prescribe schedule 5 medicines for epileptic seizures and therefore may not prescribe benzodiazepines or the required doses of phenobarbital.[5,6] Medical practitioners giving verbal instructions to a pharmacist must provide a written prescription within 7 days of the instruction. There is no legislated provision for verbal instruction to a nursing sister.
- Most Emergency Medicine Services (EMS) staff only have Basic Life Support training and are not authorised to administer Schedule 5 medicines (anecdotal information).

<u>Children < 13 years of age</u>

[5] Medicines and Related Substances Act 101 of 1965

[6] Consolidated Schedules (6 September 2024) available from https://www.sahpra.org.za

- Phenobarbital, tablets crushed via nasogastric tube (NGT) 20mg/kg does not permit a repeat dose due to the time taken to reach therapeutic levels and therefore the risk of overdosing and causing respiratory depression. However, levetiracetam, oral via NGT has been included and may be administered after phenobarbital has been given if necessary.
- At PHC level, there is no intravenous second level treatment (IM/IV phenobarbital formulation only available on section 21). Phenytoin IV requires cardiac monitoring, which is not always available at PHC level.
- At hospital level, phenytoin, IV is the only intravenous second level treatment, with no alternative when phenytoin is not recommended, i.e., if there is suspected poisoning with cardio-toxic agents (phenobarbital, IV is not on tender and not registered in South Africa and is only available through SAHPRA section 21 bulk import application).

Adolescents and adults

- At PHC level, no second- level intravenous intervention.
- At hospital level, no intravenous alternative to phenytoin, IV.

Proposals for a way forward

Access to Schedule 5 medicines

- Engagement with the Directorate for Noncommunicable Diseases in the NDOH with respect to:
    - Training of PHC Nurses in management of status epilepticus in children, adolescents and adults.
    - Engagement with EMS regarding training of public health sector paramedics.
- Engagement with Nursing Council regarding extending Section 56(6) authorisation to include Schedule 5 medicines in status epilepticus, which can be done by updating the 1984 regulations.

Intravenous second level treatment other than phenytoin

- Revisit previous reviews of the evidence and costs for intravenous valproate for consideration for use at PHC and Hospital levels as an alternative to phenytoin, IV.
- Review safety and efficacy of levetiracetam, IV, although not registered with SAHPRA

Epilepsy

Previous STGs

The 2019 AHL, 2020 PHC level and 2023 Paediatric Hospital Level STGs differed as follows:

PHC: Comprehensive general guidance provided (general measures, assessment of poorly controlled epilepsy, information to accompany referrals). However, little to no information on epilepsy types. For children, medication guidance only provided for epilepsy with generalised tonic-clonic seizures and for children with HIV on ART. Recommendation for absence seizures is to refer. For adults, no differentiation is made between epilepsy types in treatment approach. Instead, medication guidance focussed on special population groups including women of child-bearing potential (WOCBP), pregnant women, and women with HIV.

Paediatric Hospital: Epilepsy types and specific syndromes are described, but little general guidance for overall clinical care. Medication guidance provided according to epilepsy type, with cautionary statement for valproate use in girls of child-bearing potential. Description and diagnostic (including EEG) features provided. Furthermore, the paediatric hospital STGs recommended valproate for children as a first line agent for generalised tonic and or clonic seizures; and concerns were raised about the use of valproate in these children as they transition

to child-bearing potential. A misalignment existed between the PHC, AHL and Paediatric Hospital STGs.

Adult Hospital: Same as for PHC guidance for adults, with treatment approach being according to special population groups rather than epilepsy type.
Medicine choices for epilepsy at each level of care in the previous STGs are presented in Table 4. All medicines on the EML for epilepsy are available at PHC level for at least one population group, except for levetiracetam syrup and topiramate which are only at Paediatric Hospital level and tertiary and quaternary levels (for treatment resistant epilepsy).

Table 4. Medicine treatment for epilepsy at each level of care – previous guidance

PHC – Children	Paeds Hospital	PHC – Adults and Adult Hospital
Focal seizures No specific guidance	**Focal seizures** 1st line • Carbamazepine 2nd line • Levetiracetam syrup, or • Lamotrigine, or • Topiramate	**All seizure types** 1st line • Lamotrigine 2nd line Not of child-bearing potential: • Valproate Pregnant women with HIV: • Levetiracetam Pregnant women without HIV: • Carbamazepine Stable on phenytoin: • Phenytoin Stable on levetiracetam initiated as a child/ adolescent: • Levetiracetam
Generalised Tonic Clonic (GTC) seizures 1st line • Phenobarbital (children < 6 months), OR • Carbamazepine Children with HIV on ART: • Valproate, to be switched to lamotrigine when girls reach child-bearing age	**GTC and/or clonic seizures** 1st line • Valproate OR • Phenobarbital (children < 6 months) 2nd line • Levetiracetam syrup, or • Lamotrigine tablets	
Other seizure types including absence seizures • Refer	**Absence seizures** 1st line • Valproate 2nd line • Lamotrigine tablets	
	Myoclonic seizures • Valproate	

Blue=available at PHC level for the specific indication; Orange=Paediatric Hospital level only

Revised STGs

As attached, the revised STGs for PHC, AHL and Paediatric hospital focus the treatment on epilepsy types according to the ILAE classification system, rather than special population groups. The medicine choices for each epilepsy type are presented in Table 5 (children < 13 years of age) and Table 6 (adolescents and adults). While the NICE 2022 Guideline[7] does not provide separate guidance for the two age groups, the Subcommittee separated them for pragmatic reasons, to accommodate dosing advice for children and levels of care. Medicine choices for 1st, 2nd and 3rd line treatment were decided upon using the NICE 2022 Guideline recommendations with consideration of practical implications in the South African public health sector.

The table of epilepsy syndromes in the Paediatric Hospital STG was also expanded to include recommended medicines and caution regarding medications that may cause exacerbations. Dosing was not included as all syndromes are to be managed with specialist advice.

[7] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

Table 5. Epilepsy treatment in children 1 month to ≤ 12 years (Extracted from Paediatric Hospital Standard Treatment Guidelines)

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
Focal epilepsy	With or without evolution to bilateral tonic-clonic seizures	All	Lamotrigine	Carbamazepine **OR** Levetiracetam	Consider combination therapy, or add-on topiramate	Avoid carbamazepine in children with HIV on ART due to drug-drug interactions Avoid carbamazepine and topiramate in girls who may require treatment when/ if of child-bearing potential.
Generalised epilepsy	Tonic-clonic, atonic, clonic, or tonic seizures	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam or lamotrigine (whichever not used as 1st line) **OR** Valproate	Consider combination therapy with add-on Lamotrigine, **OR** Levetiracetam, **OR** Valproate, **OR** Topiramate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. Avoid topiramate in girls who are likely to require treatment when/ if of child-bearing potential. If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
		Girls likely to need treatment after age of 10 years	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam **OR** lamotrigine (whichever not used as 1st line) **OR** Consider combination therapy with lamotrigine and levetiracetam.	Consider: Valproate **OR** Add-on Topiramate	Valproate should not be used unless lamotrigine or levetiracetam, alone or in combination, are ineffective or poorly tolerated. **If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.
	Absence	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Valproate	Lamotrigine	Levetiracetam **OR** Consider combination therapy	If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
		Girls likely to continue treatment after age of 10 years	Lamotrigine	Levetiracetam	Consider combination treatment **OR** Valproate	**If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
	Myoclonic *Confirm diagnosis and discuss management with a specialist in all cases*	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Valproate	Levetiracetam	Consider Lamotrigine **OR** Topiramate, **OR** combination therapy	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
	Myoclonic (Continued)	Girls likely to continue treatment after age of 10 years	Levetiracetam	Lamotrigine	Consider Topiramate **OR** Combination therapy **OR** Valproate	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. **If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.
Combined generalised and focal epilepsy OR Unknown/unclassified *Discuss clinical presentation and management with a specialist in all cases*						
	NOTE: » Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV. » Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. » *Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus. » **If valproate is used, acknowledgment of risk must be obtained annually, even if not of child-bearing potential.** https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf » **Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.**					

Table 6. Epilepsy treatment in adolescents and adults (Extracted from Adult Hospital Level Standard Treatment Guidelines)

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
Focal epilepsy	With and without evolution to bilateral tonic-clonic seizures	Adolescent boys, men and women not able to have children	Lamotrigine	Carbamazepine **OR** Levetiracetam	Consider combination treatment or add-on topiramate	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Consider Carbamazepine **OR** Combination of lamotrigine and levetiracetam **OR** add-on topiramate	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
Generalised epilepsy	Tonic-clonic, atonic, clonic or tonic seizures	Adolescent boys, men and women not able to have children.	Lamotrigine (low-risk) **OR** Levetiracetam (high-risk)	Lamotrigine or levetiracetam (whichever not used as first line) **OR** Valproate	Discuss with specialist Consider: Combination therapy **OR** Add-on topiramate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine (low risk) **OR** Levetiracetam (high-risk)	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Refer for specialist assessment and intervention	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated.
	Myoclonic *Confirm diagnosis and discuss management with a specialist*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR** Consider combination therapy.	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.
	Absence *e.g. Juvenile absence epilepsy or persistent childhood*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR**	These seizures may be aggravated by phenytoin or carbamazepine If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.

	absence epilepsy				Consider combination therapy.	
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy **OR** Consider valproate	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated. f valproate is used, see note below on "Acknowledgement of risk form" and effective family planning. . These seizures may be aggravated by phenytoin or carbamazepine

Combined generalised and focal epilepsy
OR
Unknown/unclassified

Discuss clinical presentation and management with a specialist in all cases.

NOTE:

- Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV.
- Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. High-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.
- **If valproate is used, acknowledgment of risk must be obtained annually, even if not of child-bearing potential. Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.** https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf

*Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.

Key changes

Key changes to the medicine treatment guidance and related concerns are as follows:

- Focal epilepsy:
    - Lamotrigine is now recommended as 1st line in all age groups. ***LoE I*** – high quality systematic review and meta-analysis (Nevitt et al., 2022),[8] with high certainty findings indicating superiority of lamotrigine compared to carbamazepine, valproate, and topiramate for treatment failure for any reason and adverse effects. There are concerns of the long initiation period placing people with ongoing seizures at risk.
    - Carbamazepine is now 2nd line in those with no child-bearing potential and/or no HIV infection even though it is inferior to levetiracetam for treatment failure for any reason and for adverse effects because of its lower cost compared to levetiracetam.
    - Levetiracetam is a 2nd line option in those where child-bearing potential is or will become a concern (as evidence suggests it has lower risk of teratogenicity than carbamazepine) and those with HIV on ART. ***LoE I*** – levetiracetam is equivalent to lamotrigine in primary outcomes of treatment failure for any reason, efficacy, and adverse effects. Rationale for proposing levetiracetam as a 2nd and not 1st line option was that lamotrigine is more affordable and does not have the neuropsychiatric side effects associated with levetiracetam (although no statistically significant difference in adverse effects found by Nevitt et al.[8])
    - Topiramate was in the Paediatric Hospital STG as a 2nd line option in focal seizures. However, no difference was found between topiramate and carbamazepine by Nevitt et al.[8] and topiramate was not considered as a monotherapy option by NICE. There are also concerns around use in WOCBP. Therefore, topiramate, was removed as a 2nd line option but add-on topiramate may be considered as a 3rd line option with specialist consultation in children, adolescents and adults (as per NICE guideline[9] recommendation, AGREE II assessment conducted by the subcommittee).
    - Valproate was not an option for focal epilepsy in our existing STGs and is only listed as a 2nd line add-on option by NICE. It therefore appears reasonable to continue without it, given the safety concerns in pregnant women and people of child-bearing potential.

- Generalised epilepsy with tonic-clonic seizures
    - No difference between levetiracetam and valproate was found by Nevitt et al. 2022 in terms of treatment failure for any reason (moderate certainty evidence). Costs of levetiracetam and valproate are similar. In addition, rapid control of seizures may be achieved, therefore is a suitable replacement of valproate as 1st line option.
    - Lamotrigine retained as a 1st line option and encouraged in patients where the long-titration period is feasible ("low-risk" patients) as there is no difference to valproate in treatment failure for any reason or adverse effects, has a favourable side effect profile and is low cost. However, Nevitt et al. found less efficacy vs valproate on network meta-analysis (no difference in efficacy on direct evidence) and long titration period mean it cannot be a stand-alone 1st option.[8]
    - Valproate is a 2nd line option in those with no child-bearing potential. Although the NICE 2022 Guideline lists valproate as a 1st line option, the supporting evidence is of moderate certainty and there is evidence of effectiveness for other ASMs (lamotrigine and levetiracetam). Additionally, the NICE 2022 Guideline provides for two specialists

[8] Nevitt et al. (2022). Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database of Systematic Reviews*. DOI: 10.1002/14651858.CD011412.pub4.
[9] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

to concur regarding the need for valproate in individual patients, a process which is not accessible in South Africa.
    - Add-on topiramate included as a 3rd line option with specialist consultation (insufficient evidence to support topiramate in monotherapy).

- Generalised epilepsy with myoclonic seizures
    - Evidence base is weak, and the subcommittee has not been able to examine the evidence fully. Decision-making influenced by NICE guidance[10] (which is based largely on extrapolation of results for generalised tonic-clonic seizures which recommend valproate as 1st line option) and expert opinion on the subcommittee.
    - Valproate replaced by levetiracetam as 1st line recommendation for girls likely to need treatment when of child-bearing potential, because of safety considerations rather than efficacy.
    - Myoclonic seizures usually occur in epilepsy syndromes, often associated with severe to profound intellectual disability, where child-bearing potential is not a concern.[11] Therefore, it does not seem reasonable to withhold valproate in these patients.

- Generalised epilepsy with absence seizures
    - Valproate recommended as 1st line in those with no child-bearing potential. Based on results for treatment of childhood absence epilepsy (CAE) by Glauser et al. 2013[12], a high quality RCT which dominates the findings of the NICE 2022 evidence review. Comparing ethosuximide, valproate and lamotrigine, Glauser et al. found:
        - Efficacy at:
          16 or 20 weeks - Eth 53% (81/154) vs Valp 58% (85/146) vs Lam 30% (43/146)
          12 months - Eth 47% (70/150) vs Valp 44% (64/146) vs Lam 21% (31/146)
        - Intolerable adverse effects at:
          16 or 20 weeks - Eth 24% (37/154) vs Valp 24% (35/146) vs Lam 17% (25/146);
          at 12 months - Eth 25% (38/154) vs Valp 33% (48/146) vs Lam 20% (29/146)
        - Inattention at:
          16 or 20 weeks - Eth 33% (35/106) vs Valp 49% (52/106) vs Lam 24% (25/104)
          12 months Eth 29% (20/70) vs Valp 56% (34/61) vs Lam 27% (8/30)

      As ethosuximide is not available in the public sector and is too expensive for it to be made available, valproate is the next best choice.
    - Lamotrigine recommended for girls who may need treatment over the age of 10 years. Based on results from Glauser et al.[12] indicating at least some efficacy in CAE and to prevent continued use once of child-bearing potential. However, lamotrigine as 1st line for CAE is not acceptable to paediatric neurologists in girls or boys as it is less effective than valproate, and the time taken to establish response to treatment is too long (3 – 6 months). Evidence for efficacy of lamotrigine in juvenile absence epilepsy has been deferred by the subcommittee to the next review cycle.
    - Levetiracetam included as a 3rd line option (2nd line if child-bearing potential) based on weak evidence of efficacy vs placebo in one small RCT assessed by NICE guideline[13].

- Epilepsy Syndromes

[10] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[11] International League Against Epilepsy. EpilepsyDiagnosis.org. 30 June 2024. Available at https://www.epilepsydiagnosis.org/

[12] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, Mattson R, French JA, Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013 Mar;54(3):551-63. doi: 10.1111/epi.12074. Epub 2013 Jan 25. PMID: 23350722.

[13] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

- Description of the syndromes simplified to be more relevant to non-specialists.
- Medicine treatment now included, to facilitate access to care close to home and enable discussion between PHC/ district hospital medical practitioners and specialists, which may occur remotely.

Subcommittee deliberations

Valproate risk/benefit

The overall risk/benefit of valproate was reviewed using the following guidance/criteria**:**

- Level of care and limited indications it will be made available for. (Ensuring there is some enforcement of adherence to guidelines and how to avoid indication creep).
- Onerous dispensing – with risk/safety acknowledgement forms.
- Caution Messaging especially at PHC level of care.
- How to position recommendation (ensure access when required).
- SAHPRA regulations and requirements.
- Pharmacy at the coalface.

Valproate in girls and women of childbearing potential

There was a push for valproate to be removed from the STGs, or at the very least to not be a 1st line option for any conditions due to the concerns regarding use of valproate in pregnancy and child-bearing potential. This recommendation arose from evidence of no change in prescribing patterns despite efforts to warn clinicians, as indicated by:

- almost no response in the Western Cape to 2016 DOH warnings regarding valproate use in WOCBP the following year (Mehta et al., 2021).[14] Valproate was prescribed to 0.94% and 0.91% of all WOCBP, and 0.21% and 0.22% of pregnancies were exposed to valproate in 2016 and 2017, respectively. Over the two years, 459 pregnancies in the Western Cape were exposed to valproate. This means that, at 10% risk, 46 children would have had birth defects and, at 30% to 40% risk, between 138 and 184 children would have one or more neurodevelopmental conditions due to valproate exposure. In both years, valproate was the most used ASM among WOCBP (45.4% in 2016 and 44.4% in 2017), followed by carbamazepine and phenytoin. Lamotrigine and levetiracetam, the safest ASMs in pregnancy, were only prescribed in 8.1% and 8.9%, and 0.3% and 0.4% for 2016 and 2017, respectively.
- another Western Cape experience in which efforts to change prescribing behaviour through education and training in 2019 and 2020[15] failed to change valproate prescribing habits as assessed in 2022. Repeat awareness raising, and education on the SAHPRA risk acknowledgement form had no impact on valproate prescribing among WOCBP, as assessed in 2024, with evidence of poor compliance with the risk acknowledgement form and little justification for valproate use in clinical records.

The sentiment was that having valproate in the STGs makes it very difficult to reduce its use, even if alternative medicines are recommended as 1st line treatment. Making it a 1st line option for selected conditions would compound the effect as it creates the impression that valproate is safe to use. Cautionary statements appear to have no impact, and the SAHPRA form is not being used.

Counter arguments to this strategy for reducing valproate use were:

- There is no good alternative to valproate for certain epilepsies, including CAE, epilepsy with myoclonic seizures, and Lennox Gastaut, Dravet, and myoclonic-atonic epilepsy syndromes.

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[14] Mehta et al. (2021). Understanding and Responding to Prescribing Patterns of Valproic acid-Containing Medicines in Pregnant Women and Women of Childbearing Age in Western Cape, South Africa. *Drug Safety* 44:41–51 DOI: 10.1007/s40264-020-00987-4

[1515] Johnson Y et.al. Department of Health Pharmacy Division in collaboration with the University of Western Cape.

- While safety in pregnancy is a priority, the epilepsy must be treated optimally to reduce mortality as well as improve quality of life.
- Reasons for no reduction in valproate prescribing in the Western Cape and increased use in KZN need interrogation. Possible causes to consider include:
    - the need for a rapid treatment response among acute inpatients, for the patient's health, and to shorten the length of hospital stay and reduce bed occupancy rates, coupled with not having an alternative, rapidly acting ASM which is effective in generalised epilepsies.
    - In addition to acute treatment of generalised seizures, valproate use may be high in psychiatric patients for the same reason, especially those presenting with marked aggression such as with substance induced mood and psychotic disorders. Anecdotally, valproate is often commenced with an antipsychotic in the hope of rapidly containing aggression and disruptive behaviour.
    - Inadequate maintenance treatment of epilepsy and bipolar disorder at PHC level, resulting in repeated acute admissions requiring rapid control of symptoms.
    - A lack of confidence in using lamotrigine among prescribers, possibly related to inadequate training and experience. As well as concern of capacity to supervise incremental dosages which in children could require 2 weekly visits for 3 months, then another 3 months to confirm if agent effective or not.
    - Difficulty in implementing the long-titration period. Pharmacy instructions written on packets of different strength tablets may be confusing to patients. Effective up-titration often requires repeated clinic visits, preferably with the same practitioner at each visit. The case load and turnover of doctors at both PHC and hospital outpatient departments may preclude consistent up-titration/ cross-titration from valproate.
    - Fear that seizures will recur if valproate is changed to an alternative ASM in people who have been stabilised on valproate. Patients stabilised on valproate, including WOCBP, may also not wish to change their treatment. An analysis in Italy[16] found that valproate use remained unchanged in 70% of the cohort of WOCBP (n=528/750) who were on valproate for at least 1 year between 2014 and 2019. Intellectual disability, higher seizure frequency, and higher valproate doses were linked to valproate continuation. Valproate withdrawal from ASM polytherapy was associated with an increased risk of tonic-clonic seizure worsening (OR 2.91, 95% CI 1.09–7.77) compared to valproate continuation.
    - Many of the childhood epilepsies for which valproate is recommended will either outgrow the epilepsy before reaching child-bearing age (e.g., CAE) or will never be of child-bearing potential, mainly due to comorbid severe developmental delay (e.g., Lennox Gastaut syndrome). However, treatment of epilepsy with absence or myoclonic seizures persisting or beginning in adolescence remains a serious concern.
    - Of note epilepsy is a potentially life-threatening disease and clinicians need to be enabled to offer optimal care for their patients.

Valproate use in boys and men

- The reproductive risks of valproate use in men and associated precautionary measures needed in South Africa were deliberated briefly, noting that the UK Medicines and Healthcare Products Regulatory Agency (MHRA) has issued precautionary contraceptive advice regarding valproate use in men[17] and has included men in its recommendation that "valproate must not be started in new patients (male or female) younger than 55 years,

[16] Esposto et al. (2025). Valproic acid discontinuation in girls and women of childbearing age with epilepsy: An Italian multicenter retrospective study on prescribing patterns and outcomes. *Epilepsia.* 00:1–11 DOI: 10.1111/epi.18281
[17] NICE. Valproic acid use in men: as a precaution, men and their partners should use effective contraception. 5 September 2024. Available at: https://www.gov.uk/drug-safety-update/valproic acid-use-in-men-as-a-precaution-men-and-their-partners-should-use-effective-contraception

unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply."[18]

The following evidence of possible harm was discussed:

- A retrospective observational study, combining data from multiple registry databases in Norway, Denmark and Sweden.[19] Cumulative risk of neurodevelopmental disorders ranged from 4.0% to 5.6% in the valproate treated group versus 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy treated group (pooled adjusted hazard ratio 1.50, 95% CI 1.09 to 2.07). Of note:
    - this potential risk is much lower than the up to 30-40% risk of neurodevelopmental disorders in children born to mothers taking valproate during pregnancy and therefore may not warrant the same level of urgency.
    - the study did not include an untreated group and background risk in this patient population is therefore unknown
    - while an increased risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception is possible, the causal role of valproate is not confirmed.
    - the European Medicines Agency is currently reviewing data regarding the risk to offspring of men taking valproate,[20] and has issued the following statement "Male patients being treated with valproate should not stop taking their medicine without talking to their doctor, as their epilepsy or bipolar disorder could become worse. Sudden discontinuation of treatment for epilepsy could trigger seizures. Patients who have any questions about their treatment should speak to their healthcare professional."
- A registry linked "nationwide cohort study in Denmark comprising 1 235 353 children [born between 1997 and 2017], including 1336 children born to fathers who filled prescriptions for valproate during spermatogenesis, found no association between paternal valproate use and risk of major congenital malformations or neurodevelopmental disorders, including autism spectrum disorder."[21]
- An observational prospective study reviewed 17 infertile men with epilepsy who were switched from valproate to levetiracetam or lamotrigine.[22] Switching was associated with improved sperm counts (p=.06), total motility (p=.02), non-progressive motility (p=.03) and reduced sperm head defects (p=.03). Spontaneous pregnancies occurred in three of the 17 couples during the follow-up period.
- A meta-analysis of preclinical and clinical data concerning the impact of valproate on male fertility:[23]
    - Preclinical studies (n=112 animals): decreased sperm count and sperm motility, and increased percentage of abnormal sperm found in treated vs control groups.
    - Clinical studies (n=274 men): significant reduction in sperm motility (SMD = -1.62, 95% CI: -2.81 to -0.43, P = 0.033) but non-significant decreased sperm count and increased percentage of abnormal sperm in intervention vs control groups.

[18] NICE. Valproic acid (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age**. 22 January 2024.**Available at: https://www.gov.uk/drug-safety-update/valproic acid-belvo-convulex-depakote-dyzantil-epilim-epilim-chrono-or-chronosphere-episenta-epival-and-syonellv-new-safety-and-educational-materials-to-support-regulatory-measures-in-men-and-women-under-55-years-of-age#advice-for-healthcare-professionals https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproic acid-medicines-prac-recommends-precautionary-measures.

[19] Potential risk of neurodevelopmental disorders in children born to men treated with valproic acid medicines: PRAC recommends precautionary measures. 12 January 2024. Available at: https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproic acid-medicines-prac-recommends-precautionary-measures

[20] European Medicines Agency (EMA). EMA review of data on paternal exposure to valproic acid. 16 August 2023. Available at: https://www.ema.europa.eu/en/news/ema-review-data-paternal-exposure-valproic acid

[21] Christensen et al. 2024. Valproic acid Use During Spermatogenesis and Risk to Offspring. *JAMA Network Open.* 7(6): e2414709. DOI:10.1001/jamanetworkopen.2024.14709

[22] Markoula et al. 2020. An open study of valproic acid in subfertile men with epilepsy. *Acta Neurol Scand*. 142:317–322. DOI: 10.1111/ane.13311

[23] Asghar et al. 2024. Understanding the impact of valproic acid on male fertility: insights from preclinical and clinical meta-analysis. BMC Pharmacology an d Toxicology 25:69 DOI:10.1186/s40360-024-00791-1

The subcommittee's conclusion was that the evidence of harm to children from valproate use in men was very weak and did not warrant prescribing limitations such as those recommended for WOCBP. While valproate use may negatively affect fertility, this could be managed with a recommendation to advise the patient, and to use lamotrigine or levetiracetam if needed.
Therefore, medicine treatment guidance has been separated for boys and men vs girls and WOCBP in the STGs (see Tables 5 and 6 above).

Ensuring compliance with SAHPRA recommendations for valproate

Discussion focussed on ways to ensure that completion of the SAHPRA acknowledgement of risk form if valproate is used in girls and WOCBP. Possibilities included simplifying the form (discussions are underway between the EDP and SAHPRA), restricting valproate use to hospital level services and specialist prescription, or training pharmacists at hospital and district level to not dispense if no signed form is attached to the prescription and to discuss with the prescriber in such cases.

If it is a way forward, a simplified form should be coordinated by the regulator. It is unclear whether the simplified form in the Western Cape has reduced valproate prescribing where alternative medicines may be used, improved counselling of the patient and/or caregiver, and appropriate contraception use.

Restricting to hospital level and specialist initiation in this population group may be an option (waiting lists are long and travel is not always available or convenient). Most of the epilepsies for which valproate is recommended 1st line should all be managed in consultation with a specialist, and Part B of the SAHPRA acknowledgement of risk form[24] must be signed by a specialist. The problem is that to prevent breaks in maintenance treatment, valproate should ideally be available at PHC level, as the most accessible point of care. Additionally, typical CAE should be diagnosed and managed by PHC level medical doctors (where they are available), as the condition is not complex and improved coverage is needed.

Valproate will be available at PHC level for epilepsies in boys and men and for bipolar disorder. Therefore, another strategy is that pharmacists at all levels of care would not dispense valproate for girls and WOCBP without a signed motivation or a copy of the risk acknowledgement form attached to the prescription. What is then required is that hard copies of the form should be available at all levels of care, in all relevant clinics.

Cost considerations

Using 2024 tender prices and defined daily dosing (DDD), the cost of levetiracetam is similar to valproate (Table 7). Therefore, expanding use of levetiracetam as a replacement for valproate is unlikely to affect overall expenditure. However, lamotrigine is the cheapest option.

[24] https://www.sahpra.org.za/document/valproic acid-annual-risk-acknowledgement-form/

Table 7. Antiseizure medicine costs per Defined Daily Dose (DDD) at December 2024 tender prices

Medicine	Strength		Formulation	Pack size	Price 2024	Cost/tablet or ml	DDD (in mg)	Tablets /mls in a DDD	Cost of 1 DDD	Cost for 28 days
Carbamazepine	20	mg/ml	Suspension	250	R 126,79	R 0,51	1000	50	R 25,36	R 710,02
Carbamazepine	200	mg	Tablet	28	R 15,64	R 0,56	1000	5	R 2,79	R 78,20
Carbamazepine	200	mg	Tablet	56	R 35,75	R 0,64	1000	5	R 3,19	R 89,38
Carbamazepine	200	mg	Tablet	56	R 31,96	R 0,57	1000	5	R 2,85	R 79,90
Carbamazepine	200	mg	Tablet	84	R 49,81	R 0,59	1000	5	R 2,96	R 83,02
Carbamazepine	200	mg	Tablet	84	R 51,72	R 0,62	1000	5	R 3,08	R 86,20
Carbamazepine	400	mg	Tablet	28	R 52,50	R 1,88	1000	3	R 4,69	R 131,25
Lamotrigine	25	mg	Tablet	56	R 18,20	R 0,33	300	12	R 3,90	R 109,20
Lamotrigine	50	mg	Tablet	56	R 18,20	R 0,33	300	6	R 1,95	R 54,60
Lamotrigine	100	mg	Tablet	56	R 36,68	R 0,66	300	3	R 1,97	R 55,02
Lamotrigine	200	mg	Tablet	56	R 71,18	R 1,27	300	2	R 1,91	R 53,39
Levetiracetam	250	mg	Tablet	30	R 23,46	R 0,78	1500	6	R 4,69	R 131,38
Levetiracetam	500	mg	Tablet	30	R 43,24	R 1,44	1500	3	R 4,32	R 121,07
Levetiracetam	750	mg	Tablet	30	R 64,40	R 2,15	1500	2	R 4,29	R 120,21
Phenobarbital	30	mg	Tablet	28	R 5,42	R 0,19	100	3	R 0,65	R 18,07
Phenobarbital	30	mg	Tablet	56	R 9,91	R 0,18	100	3	R 0,59	R 16,52
Phenobarbital	30	mg	Tablet	84	R 15,54	R 0,19	100	3	R 0,62	R 17,27
Phenytoin	100	mg	Capsule	100	R 66,19	R 0,66	300	3	R 1,99	R 55,60
Phenytoin	100	mg	Tablet	84	R 54,73	R 0,65	300	3	R 1,95	R 54,73
Topiramate	25	mg	Tablet	60	R 25,46	R 0,42	300	12	R 5,09	R 142,58
Topiramate	50	mg	Tablet	60	R 30,98	R 0,52	300	6	R 3,10	R 86,74
Topiramate	100	mg	Tablet	60	R 49,72	R 0,83	300	3	R 2,49	R 69,61
Valproic acid	40	mg/ml	Syrup	300	R 133,11	R 0,44	1500	38	R 16,64	R 465,89
Valproic acid	100	mg	Dispersible tab	100	R 155,95	R 1,56	1500	15	R 23,39	R 654,99
Valproic acid/Valproic acid	200	mg	Tablet	100	R 69,82	R 0,70	1500	8	R 5,24	R 146,62
Valproic acid/Valproic acid	200	mg	Tablet	56	R 44,53	R 0,80	1500	8	R 5,96	R 166,99
Valproic acid/Valproic acid	300	mg	Tablet	100	R 90,56	R 0,91	1500	5	R 4,53	R 126,78
Valproic acid/Valproic acid	300	mg	Tablet	56	R 56,72	R 1,01	1500	5	R 5,06	R 141,80
Valproic acid/Valproic acid	500	mg	Tablet	100	R 136,77	R 1,37	1500	3	R 4,10	R 114,89
Valproic acid/Valproic acid	500	mg	Tablet	56	R 85,30	R 1,52	1500	3	R 4,57	R 127,95

Education and training

Lack of expertise among general medical practitioners in diagnosing and managing epilepsy is concerning, especially at PHC level. The BPNA (British Paediatric Neurology Association) has developed a Paediatric Epilepsy Training (PET)[25] course which has been facilitated and endorsed by ILAE for international roll-out. In addition, ILAE has piloted an Epilepsy Training in Adult Medicine (ETAM) course which should also be widely available in Africa. While the NDOH knowledge hub webinars may be used to disseminate the STGs, there is a need to explore other options for more widespread training.

Medicine treatment recommendations

No new medicines have been added to treatment recommendations. However, there are changes in indications and hierarchy of medicine choices. Points considered:

- Valproate recommended as 1st line recommendation for absence seizures in girls ≤10 years, Lennox Gastaut and Dravet syndromes. NICE guidance has retained valproate as a 1st line option for various epilepsies based on evidence of efficacy. NICE has not used hierarchy of choice as a mechanism for discouraging valproate use but has emphasized the need to trial other 1st line options in girls and WOCBP. Our guidelines differ in that we do not tend to provide alternative options in each category unless they are equivalent, and choice is influenced by availability.
- Affordability of expanding levetiracetam vs lamotrigine use.
- Expansion of topiramate indications to other epilepsies and age groups (is Paediatric Hospital at present for focal epilepsy and indicated for refractory epilepsy at tertiary level). It is always as a 3rd line treatment with specialist consultation, to facilitate care of treatment resistant epilepsy. Evidence for use is not strong, and inappropriate prescribing should be prevented.

Monitoring and evaluation

Medicine utilisation monitoring should be coupled with some form of treatment outcome monitoring (e.g., epilepsy rehospitalisation). This may require expansion of national indicators to include epilepsy. The Affordable Medicines directorate is in the process of approaching relevant NDOH stakeholders to discuss the issue.
Included in stakeholder consultation, is the need to expand education and training programs.

Recommendations for review in the next review cycle

- Consider a full GRADE Adolopment process of NICE guidelines.
- Future review cycles, continue review of generalised epilepsy with tonic-clonic seizures as low-risk and high-risk groups.
- Review motivation and evidence for IV levetiracetam, however not yet registered in South Africa.
- Re-evaluation of previous reviews on use of IV valproate in status epilepticus.
- Evidence for efficacy of lamotrigine in juvenile absence epilepsy.
- Affordability of expanding levetiracetam vs lamotrigine use.
- Need for rescue therapy in specific high-risk cases where the diagnosis of epilepsy is not confirmed is still to be discussed by the subcommittee.

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[25]British Paediatric Neurology Society. Paediatric Epilepsy Training (PET). Available at: https://courses.bpna.org.uk/index.php?page=paediatric-epilepsy-training#:~:text=Paediatric%20Epilepsy%20Training%20(PET)%20is,is%20now%20being%20established%20worldwide.

- Review occupational therapy for the epilepsy STGs in the next review cycle.
- Epilepsy has functional implications that require screening and intervention from a rehabilitation multidisciplinary team to prevent a disability. NEMLC advised that a thorough review regarding occupational therapy and epilepsy be conducted in the next review cycle.

Appendix A: AGREE II assessment on NICE guidelines:

AGREE II assessment scores

Epilepsies in children, young people and adults (April 2022 - Updated 2025)

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	7	7	7	7	159
Appraiser 2	7	7	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	5	7	7	6	6	7	154
Item Total	14	14	13	13	13	14	14	14	14	14	14	14	13	13	14	14	14	12	14	14	13	13	14	313
Domain Total	41			40			110								42			53				27		313
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**97%**			**94%**			**98%**								**100%**			**94%**				**96%**		**97%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

Maximum possible score = 7 (highest score) x no. of items x no. of appraisers
Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers

Score for each domain

Obtained score - minimum possible score / Maximum possible score - minimum possible score X 100

NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

South African National Essential Medicine List
Primary Health Care (PHC), Adult Hospital Level (AHL), Paediatric Hospital Level Medication Review Process
Component:
CARBAMAZEPINE IMMEDIATE VERSUS CONTROLLED RELEASE

EVIDENCE SUMMARY

Date: February 2025

Query: Guidance and approval are required from NEMLC as to whether the NDoH should tender for carbamazepine immediate release and controlled release/modified release:

- separately and awarded separately (as separate specification items)

OR

- as an either-or option and if the least expensive option should be awarded (noting the need for some immediate release formulation for titration etc).

Background

The Affordable Medicines Directorate (AMD) of the National Department of Health is currently preparing for the next tender for solid dosage forms. A query arose during the bid specification process as to how carbamazepine immediate release and modified/controlled release preparations should be tendered for i.e. both provided on tender, or an either-or option as summarised above. This is a historic query raised by the provinces.

Carbamazepine modified release history

- Carbamazepine 400mg tablet, 28 tablets:
  - tender specification was first added in 2015 (note only 400mg specification; not specified as modified release). At the time the item was not awarded on contract.
- Carbamazepine; 400mg; Tablet, MR; 28 tablets:
  - awarded on contract in 2019 – RT89-2019 (*1 May 2019 – 30 April 2021*
  - Not awarded on next tender: HP09-2021 (no bids received for this specification) – item canceled.
  - Awarded on current tender HP09-2023 (ending in April 2026).
  - Note specification always advertised as just 400mg tablet, but only modified release tablets offered.

Historically the carbamazepine immediate release (IR) and modified/controlled release (CR) preparations were tendered for as an either-or option based on previous NEMLC guidance that there is no preference for either product, or the cheaper product should be made available. The Bid Specification Committee however indicated that there is still usage of the modified/controlled release preparation across some of the provinces accessed through the named patient motivation process. In preparation for the next solid dosage form tender, the Essential Drugs Programme is requesting confirmation from NEMLC, that the carbamazepine immediate release and modified/controlled release preparations still be tendered for as an either-or option. Availability of medicines on a national contract facilitates easier access in terms of procurement for all provinces. It was noted that the next Bid Specification meeting is scheduled for 11 February 2025 and the NEMLC meeting will be held on 27 February 2025. Feedback can be provided to the Bid Specification Committee following the February 2025 NEMLC meeting.
Currently there is varied use across the country (see procurement summary below), but feedback during the tender meetings indicate that the provinces prefer the modified release.

The matter was also tabled at the 20 December 2024 epilepsy SC meeting where members indicated preference for tendering separately as there might be instances where the controlled release/modified release is preferred to the immediate release e.g. (1) in young children where adverse effects of drowsiness occurring in the school day could

impact adherence and (2) where patients have already been initiated on a on formulation and switching might not be desired. It was also noted that the issue of offering two different formulations raises concerns around equity as some provinces are purchasing the controlled release preparation while others do not, and some provinces offer the immediate release preparation mainly while the controlled release preparation is maintained through good governance on a named patient basis only.

Purpose of this document

To outline:

- The Query (as above)
- Background (as above)
- Indications of Carbamazepine in the STGs
- Tabulate the pharmacokinetic differences of both options
- External comments related to carbamazepine that might relate to type of formulation **(**PHC CNS conditions and AHL Neurological Disorders)
- National surveillance data for carbamazepine
- Adverse events of carbamazepine
- Outline current medicine health product list (MHPL) prices for carbamazepine

Current indications for Carbamazepine in the Standard Treatment Guidelines

Medicine	Children and adolescents		Adults	
	PHC	Hospital	PHC	Hospital
Carbamazepine, oral (suspension and tablets)	**Central Nervous System Conditions Chapter:** Epilepsy in children (generalised tonic-clonic seizures) Children ≤12 years of age:	**The Nervous System Chapter** Focal (*partial*) seizures - 1st line	**Central Nervous System Conditions Chapter:** Focal (partial) seizures - 2nd line - acute and chronic Mx - HIV negative people only	**Neurological Disorders Chapter:** Focal (partial) seizures - 2nd line - acute and chronic Mx - HIV negative people only
	Pain Chapter Neuropathic Pain - Post-herpetic neuralgia - Trigeminal neuralgia		**Central Nervous System Conditions Chapter:** Generalised tonic clonic seizures - 2nd line - acute and chronic Mx - HIV negative people only	**Neurological Disorders Chapter:** Generalised tonic clonic seizures - 2nd line - acute and chronic Mx - HIV negative people only
			Central Nervous System Conditions Chapter: - Women of child-bearing potential and pregnant women- HIV-uninfected women	**Neurological Disorders Chapter:** - Women of child-bearing potential and pregnant women- HIV-uninfected women

Immediate release vs-controlled release/modified release carbamazepine

Summary of a Cochrane review: Taken from (Powell et al., 2017)[1]

- Objective:
    - To determine the efficacy of immediate-release (IR) carbamazepine versus controlled-release (CR) carbamazepine in patients diagnosed with epilepsy.
- Review questions:
    1. For newly diagnosed patients commencing carbamazepine, how do IR and CR formulations compare for efficacy and tolerability?
    2. For patients on established treatment with IR carbamazepine but experiencing unacceptable adverse events, what is the effect on seizure control and the tolerability of a switch to a CR formulation versus remaining on the immediate release formulation?
- Ten trials (296 participants) fulfilled the criteria for inclusion in this review.
- Only one study had a low risk of bias.
- Two studies had a high risk of bias while 7 studies were rated as unclear risk of bias.
- One trial included patients with newly diagnosed epilepsy and nine included patients on treatment with immediate release carbamazepine
- Eight trials reported heterogeneous measures of seizure frequency with conflicting results.
- A statistically significant difference was observed in only one trial, with patients prescribed controlled release carbamazepine experiencing fewer seizures than patients prescribed immediate release carbamazepine
- Nine trials reported measures of adverse events. (see section below – Adverse events of Carbamazepine: for more detailed information from these trials)
- Data from trials do not confirm or refute an advantage for CR carbamazepine over IR carbamazepine for seizure frequency or adverse events in patients with newly diagnosed epilepsy.
- For trials involving epilepsy patients already prescribed IR carbamazepine, no conclusions can be drawn concerning the superiority of CR carbamazepine with respect to seizure frequency.
- ***There is a trend for CR carbamazepine to be associated with fewer adverse events when compared to IR carbamazepine.***
- ***A change to CR carbamazepine may therefore be a worthwhile strategy in patients with acceptable seizure control on IR carbamazepine but experiencing unacceptable adverse events.***
- The included trials were of small size and of poor methodological quality limiting the validity of this conclusion.
- Randomised controlled trials comparing CR carbamazepine to IR carbamazepine and using clinically relevant outcomes are required to inform the choice of CR carbamazepine preparation for patients with newly diagnosed epilepsy.

External comments (PHC CNS and AHL Neurological Disorders)

The following external comment which could be related to formulation was raised about carbamazepine during the most recent (October 2024) call for comment on the PHC CNS conditions and AHL Neurological disorders chapters.

Pharmacological Agents: Carbamazepine

- The carbamazepine we have available is very toxic and very seldom do patients tolerate a total dose of 400mg per day. Hence compliance is very poor. Carbamazepine CR or oxcarbazepine are better alternatives to CBZ.

National surveillance data for carbamazepine

Table 1 summarises national procurement for the period January 2019 to December 2024 (6 years).

Table 1: National procurement for the period January 2019 to December 2024 (6 years)

Medicine Pack Short Description	Units Procured from January 2019 to December 2024	Average monthly units over 6-year period	% Total National Carbamazepine Procurement
Carbamazepine; 200mg; Tablet; 56 Tablets	7405276	102851	37.18%
Carbamazepine; 200mg; Tablet; 84 Tablets	8981036	124737	45.10%
Carbamazepine; 200mg; Tablet; 28 Tablets	2617380	36353	13.14%
Carbamazepine; 400mg; tablet, CR; 28 Tablets	607049	8431	3.05%

Carbamazepine; 100mg/5ml; Suspension; 250 ml	304439	4228	1.53%

According to the data provided from the national surveillance centre, three provinces (NC, EC and MP) contributed to the total national usage of carbamazepine 400mg controlled release (28 tablets) for the 6-year period - January 2019 to December 2024.

Table 2: Provincial Procurement Breakdown of Carbamazepine 400mg controlled release (28 tablets) for the period January 2019 to December 2024

Province	Total Units Procured from January 2019 to December 2024	% of Total
Northern Cape	10	0.002%
Eastern Cape	22774	3.752%
Mpumalanga	584265	96.247%
Total National Usage	607049	

Adverse events of carbamazepine

Although the current data as reported by Powell et.al. is unable to confirm or refute an advantage of CR carbamazepine over IR carbamazepine, there was a trend for CR carbamazepine to be associated with fewer adverse events. See individual studies adverse event findings below.

Newly diagnosed patients:	Established epilepsy
Nag et.al. 1998[26] Unblinded parallel trial (20 adult patients with newly diagnosed epilepsy) – 20-day study period: • Four adverse events were reported in patients prescribed immediate release carbamazepine: diplopia, rash, and two reports of sedation. • Two adverse events were reported in patients prescribed controlled release carbamazepine, sedation and diplopia.	Studies using scale scores to assess adverse events: • McKee 1991[27]: (N=25 participants, 21 completed study) ▪ Cognitive adverse event scores at one hour were significantly lower with controlled release carbamazepine as compared to immediate release. ▪ Reaction times were significantly shorter at one and four hours with controlled release carbamazepine as compared to immediate release. • Aldenkamp 1987[28] (N=11 participants) ▪ Reported increased performance in various tests of cognitive function in patients taking controlled release carbamazepine. *(The statistical significance of this result was not reported)* • Persson 1990[29] (N=21 participants, 20 completed study) ▪ Reported lower scores on a combined systemic toxicity and neurotoxicity scale in patients taking controlled release carbamazepine as compared to immediate release. (*The difference was statistically significant)* Studies reporting individual numbers of adverse events • Anonymous 1995[30] (N=101 participants, 87 completed study) ▪ No statistically significant differences between adverse events in immediate release and controlled release groups: ▪ 6 adverse events were reported by 4 patients with prescribed controlled release carbamazepine (dizziness (2 patients), diplopia, headache, nausea, vomiting).

26 Nag D, Garg RK, Agarwal A. A comparative evaluation of pharmacokinetics of conventional and slow-release carbamazepine formulation in newly treated patients of epilepsy: a random evaluation. Journal of the Association of Physicians of India 1998;46(2):185-8.

27 McKee PJW, Blacklaw J, Butler E, Gillham RA, Brodie MJ. Monotherapy with conventional and controlled release carbamazepine: a double blind, double dummy comparison in epileptic patients. British Journal of Clinical Pharmacology 1991;32(1):99-104.

28 Aldenkamp AP, Alpherts WC, Moerland MC, Ottevanger N, Van_Parys JA. Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 1987;28(5):507-14.

29 Persson LI, Ben-Menachem E, Bengtsson E, Heinonen_E. Differences in side effects between a conventional carbamazepine preparation and a slow-release preparation of carbamazepine. Epilepsy Research 1990;6(2):134-40.

30 Anonymous. Double-blind crossover comparison of Tegretol-XR and Tegretol in patients with epilepsy. The Tegretol OROS Osmotic Release Delivery System Study Group. Neurology 1995;45(9):1703-7.

	▪ 5 adverse events were reported by 5 patients with immediate release carbamazepine (dizziness, drowsiness, hand-tremor, stomach cramps and vomiting). • Reunanen 1990[31] (N=21 participants, 18 completed study) ▪ 19 adverse events with immediate release carbamazepine therapy compared to 12 with controlled release carbamazepine. The differences were statistically different for dizziness (7 times in immediate release group compared to 1 time in controlled release group). Studies reporting only number of adverse events (no details on event type) • Sivenius 1988[32] (N=24 participants, 22 completed study) ▪ 4 patients in each treatment group (IR and CR carbamazepine) experienced adverse events. • Canger 1990[33] (N=48 participants) ▪ 26 patients reported adverse events with IR carbamazepine and 6 reported adverse events with CR carbamazepine. This difference was reported as statistically significant.

A request was made to South African Health Products Regulatory Authority (SAHPRA) for information around reports on adverse events associated with either CR or IR carbamazepine.

The SAHPRA VigiFlow Safety database showed that there had been 238 adverse reactions in 118 cases with IR carbamazepine (154 serious), and 42 adverse reactions in 23 cases with CR carbamazepine (35 serious).
See annexure 1 for full information provided.

Cost considerations

December 2024 tender prices,[2] are outlined in the table 3 below. Where the award is split weighted averages were calculated.

[31] Reunanen_M, Heinonen_E, Antila_M, Jarvensivu_P, Lehto_H, Hokkanen_E. Multiple dose pharmacokinetic study with a slow-release carbamazepine preparation. Epilepsy Research 1990;6(2):126-33.
[32] Sivenius_J, Heinonen_E, Lehto_H, Jarvensivu_P, Anttila_M, Ylinen_A, et al. Reduction of dosing frequency of carbamazepine with a slow-release preparation. Epilepsy Research 1988;2(1):32-6.
[33] Canger_R, Altamura_AC, Belvedere_O, Monaco_F, Monza_GC, Muscas_GC, et al. Conventional vs controlled release carbamazepine: a multicentre, double blind, crossover study. Acta Neurologica Scandinavica 1990;82(1):9-13.

Table 3: Medicine Health Product List Prices for Carbamazepine (December 2024)

**Usual maintenance dose: 600 – 1200mg/day[3] (800mg/day used for comparison purposes)*

Medicine pack short description	Quantity Awarded	Pack size	Price (Rand)	Split %	Price Per Tablet/mL (Rand)*	Usual Maintenance dose	Cost per day (Rand)*	Cost per month (28 days) (Rand)*	Comments
Carbamazepine; 200mg; Tablet; 28 Tablets	1 583 492	28	R15,18	100	0,54	800mg daily	R2.16	R60,48	Least Expensive Per Month
Carbamazepine; 200mg; Tablet; 56 Tablets	805 366	56	R34,69	25	0.58**	800mg daily	R2.32	R64,96	Weighted Average calculated based on supplier split
Carbamazepine; 200mg; Tablet; 56 Tablets	2 416 097	56	R31,39	75		800mg daily			
Carbamazepine; 200mg; Tablet; 84 Tablets	1 145 004	84	R48,41	40	0.59**	800mg daily	R2.36	R66.08	Weighted Average calculated based on supplier split
Carbamazepine; 200mg; Tablet; 84 Tablets	1 717 505	84	R50,20	60		800mg daily			
Carbamazepine; 400mg; tablet, cr; 28 Tablets	692 969	28	R52,5	100	1,88	800mg daily	R3.76	R105.28	Controlled release tablet 1g dose on 400mg would not be advised as should not break tablet
Carbamazepine; 100mg/5ml; Suspension; 250 ml	179 463	250	R126,79	100	0,51	800mg daily	R20.40	R571.20	Liquid Option

*Rounded to 2 decimal places

**Weighted Average:

Weighted Average: Carbamazepine; 200mg; Tablet; 56 Tablets = R32.22

Weighted Average: Carbamazepine; 200mg; Tablet; 84 Tablets = R49.48

Price of 2 x 200mg (28s) = R1.08 (80 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 2 x 200mg (56s) = R1.16 (72 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 2 x 200mg (84s) = 1.18 (70 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 1 x 400mg CR = R1.88

Conclusion

- There is a trend to better tolerance and less adverse events with CR carbamazepine, particularly in the area of drowsiness and dizziness.
- Adherence with CR carbamazepine is considered better, however there are limited studies to support this, and it is no longer being investigated as a question of interest or relevance internationally.
- Convenience benefits of less frequent daily dosing may be applicable to school going children or the adults needing to focus at work (where drowsiness hinders this), particularly those operating machinery etc.
- The current pricing indicates that CR carbamazepine is still approximately 30% more than comparative IR carbamazepine, however no assessment of cost-effectiveness, have been undertaken to assess the potential benefits of less adverse events, better adherence and compliance.

Proposal

- The Epilepsy Subcommittee recommends that both IR and CR carbamazepine be made available on National Tender. It is proposed that CR carbamazepine be specifically utilised for patients experiencing adverse events to the IR carbamazepine, as well as those of school going age, and those operating machinery.

NEMLC Recommendation: 27 February 2025

NEMLC recommended that both immediate release (IR) and controlled release (CR) carbamazepine be tendered for and that both IR and CR carbamazepine be tendered for and the least expensive option be selected for use.

[1] Powell G, Saunders M, Rigby A, Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database Syst Rev. 2016 Dec 8;12(12):CD007124. doi: 10.1002/14651858.CD007124.pub5. PMID: 27933615; PMCID: PMC6463840.

[2] NDoH. Medicine Health Product List. December 2024

[3] University of Cape Town, Faculty of Health Sciences, Division of Clinical Pharmacology. (2024). South African Medicines Formulary (SAMF). SAMF website. https://samf-app.com

Annexure A:

Adverse Event reports from the South African Health Products Regulatory Authority (SAHPRA) (report accessed: 17 February 2025).

The SAHPRA VigiFlow Safety database showed the following:

Immediate release Carbamazepine	Controlled Release Carbamazepine
• 238 adverse reactions reported in 118 cases where carbamazepine immediate release was a suspect or co-suspect drug. • 154 adverse reactions were reported as serious.	• 42 adverse reactions reported in 23 cases wherein carbamazepine controlled release was reported as a suspect medicine. • 35 adverse event terms were reported as serious. • Tegretol CR was the reported trade name in all cases.

Adverse reaction system organ class with number reported	
Blood and lymphatic system disorders (SOC)	**2**
Lymphadenopathy	1
Neutropenia	1
Cardiac disorders (SOC)	**6**
Cardiac disorder	2
Cardiac failure	1
Myocardial infarction	2
Sinus arrhythmia	1
Endocrine disorders (SOC)	**1**
Inappropriate antidiuretic hormone secretion	1
Eye disorders (SOC)	**6**
Eye pain	1
Eye swelling	1
Photopsia	1
Vision blurred	3
Gastrointestinal disorders (SOC)	**15**
Abdominal distension	1
Abdominal pain upper	1
Constipation	1
Dysphagia	3
Food poisoning	1
Gingival swelling	1
Lip swelling	2
Mouth haemorrhage	1
Nausea	1
Oral mucosal blistering	1
Swollen tongue	1
Vomiting	1
General disorders and administration site conditions (SOC)	**38**
Chills	1
Condition aggravated	1
Death NOS	8
Drug ineffective	3
Drug interaction	1
Drug resistance	1
Fatigue	1
Feeling abnormal	1
Feeling cold	1
Feeling drunk	1
Foaming at mouth	1
Gait disturbance	1
General physical health deterioration	1

Cardiac disorders (SOC)	
Cardiac disorder (PT)	
Myocardial infarction (PT)	
Gastrointestinal disorders (SOC)	
Abdominal distension (PT)	
Abdominal pain upper (PT)	
Gastrointestinal disorder (PT)	
Mouth swelling (PT)	
General disorders and administration site conditions (SOC)	
Condition aggravated (PT)	
Death NOS (PT)	
Drug ineffective (PT)	
Enanthema (PT)	
Malaise (PT)	
Pain (PT)	
Peripheral swelling (PT)	
Hepatobiliary disorders (SOC)	
Hepatic function abnormal (PT)	
Immune system disorders (SOC)	
Hypersensitivity (PT)	
Infections and infestations (SOC)	
Lower respiratory tract infection (PT)	
Pneumonia (PT)	
Tooth abscess (PT)	
Injury, poisoning and procedural complications (SOC)	
Product use in unapproved indication (PT)	
Investigations (SOC)	
Blood alkaline phosphatase increased (PT)	
Blood glucose abnormal (PT)	
Blood testosterone increased (PT)	
Gamma-glutamyltransferase increased (PT)	
Lipids increased (PT)	
Metabolism and nutrition disorders (SOC)	
Feeding disorder (PT)	
Musculoskeletal and connective tissue disorders (SOC)	
Systemic lupus erythematosus (PT)	
Nervous system disorders (SOC)	
Cerebrovascular accident (PT)	
Dizziness (PT)	
Epilepsy (PT)	
Seizure (PT)	
Speech disorder (PT)	

Hangover	1
Hernia	1
Malaise	2
Pain	5
Peripheral swelling	1
Pyrexia	1
Swelling	1
Swelling face	2
Therapeutic response unexpected	1
Ulcer	1
Infections and infestations (SOC)	**4**
Cystitis	1
Lower respiratory tract infection	1
Pustule	1
Tooth abscess	1
Injury, poisoning and procedural complications (SOC)	**21**
Accidental exposure to product by child	2
Contraindicated product administered	1
Contusion	2
Fall	1
Hip fracture	1
Maternal exposure before pregnancy	1
Maternal exposure during breast feeding	1
Maternal exposure during pregnancy	2
Medication error	1
Overdose	1
Product prescribing issue	1
Spinal fracture	1
Toxicity to various agents	1
Upper limb fracture	2
Wrong technique in product usage process	3
Investigations (SOC)	**12**
Blood potassium decreased	1
Blood pressure abnormal	1
Blood sodium decreased	1
C-reactive protein increased	1
Drug level above therapeutic	1
Haemoglobin decreased	1
Heart rate decreased	1
Heart rate increased	1
Hepatic enzyme increased	2
Viral load increased	1
White blood cell count decreased	1
Metabolism and nutrition disorders (SOC)	**3**

Trigeminal neuralgia (PT)	1
Product issues (SOC)	**1**
Product availability issue (PT)	1
Reproductive system and breast disorders (SOC)	**1**
Priapism (PT)	1
Skin and subcutaneous tissue disorders (SOC)	**4**
Pruritus (PT)	1
Rash (PT)	1
Skin disorder (PT)	1
Skin irritation (PT)	1
Vascular disorders (SOC)	**1**
Venous occlusion	1

Feeding disorder	1
Hypokalaemia	1
Hyponatraemia	1
Musculoskeletal and connective tissue disorders (SOC)	**5**
Arthralgia	1
Arthropathy	1
Back pain	1
Muscle twitching	1
Rheumatoid arthritis	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	**2**
Lung neoplasm malignant	1
Neoplasm malignant	1
Nervous system disorders (SOC)	**52**
Aphasia	1
Ataxia	2
Balance disorder	1
Burning sensation	1
Cerebrovascular accident	1
Coma	1
Dizziness	13
Dysarthria	1
Epilepsy	3
Headache	2
Hypersomnia	2
Hypoaesthesia	2
Loss of consciousness	2
Memory impairment	1
Migraine	1
Multiple sclerosis relapse	1
Sedation	1
Seizure	12
Somnolence	2
Syncope	1
Tremor	1
Pregnancy, puerperium and perinatal conditions (SOC)	**2**
Abortion spontaneous	2
Product issues (SOC)	**1**
Product packaging issue	1
Psychiatric disorders (SOC)	**9**
Completed suicide	1
Depressed mood	1
Depression	1
Disorientation	1

Enuresis	1
Insomnia	3
Stress	1
Renal and urinary disorders (SOC)	**2**
Pollakiuria	1
Renal failure	1
Respiratory, thoracic and mediastinal disorders (SOC)	**5**
Cough	2
Lung disorder	1
Oropharyngeal pain	1
Pulmonary fibrosis	1
Skin and subcutaneous tissue disorders (SOC)	**48**
Angioedema	1
Blister	2
Drug reaction with eosinophilia and systemic symptoms	2
Erythema	1
Hyperhidrosis	1
Pruritus	1
Rash	13
Rash erythematous	1
Rash maculo-papular	3
Rash pruritic	3
Skin erosion	2
Stevens-Johnson syndrome	14
Toxic epidermal necrolysis	2
Urticaria	1
Yellow skin	1
Vascular disorders (SOC)	**4**
Ischaemia	1
Peripheral coldness	1
Thrombosis	2

Patient demographics

Adolescent	**2**
Male	2
Adult	**53**
Female	35
Male	17
Unknown	1
Child	**5**
Female	2
Male	2
Unknown	1
Elderly	**21**
Female	13

Adolescent	**1**
Male	1
Adult	**17**
Female	10
Male	7
Elderly	**12**
Female	4
Male	8
Unknown	**26**
Female	6
Male	19
Unknown	1

Male	8
Infant	**1**
Female	1
No age group	**36**
Female	20
Male	14
Unknown	2

Concomitant medications

Acetazolamide	
Acetylsalicylic acid	
Allopurinol	
Alprazolam	
Amitriptyline hydrochloride	
Amlodipine	
Amoxicillin sodium	
Clavulanate potassium	
Atenolol	
Beclometasone	
Benzydamine hydrochloride	
Chlorhexidine gluconate	
Bisoprolol fumarate	
Bromazepam	
Chloramphenicol	
Chlorpromazine	
Citalopram hydrochloride	
Clobazam	
Clonazepam	
Diazepam	
Dolutegravir sodium	
Dosulepin hydrochloride	
Enalapril	
Esomeprazole magnesium trihydrate	
Fluoxetine hydrochloride	
Flupentixol decanoate	
Folic acid	
Gabapentin	
Gentiana lutea root	
Primula spp. flower	
Rumex spp. herb	
Sambucus nigra flower	
Verbena officinalis herb	
Gliclazide	
Haloperidol	
Hydrochlorothiazide	
Hydrochlorothiazide	
Valsartan	
Indapamide	
Indometacin	
Insulin bovine	
Insulin porcine	
Insulin glargine	
Lamotrigine	
Levetiracetam	
Levothyroxine sodium	
Lorazepam	
Metformin	
Methylephedrine	
Metoclopramide hydrochloride	
Morniflumate	
Nystatin	
Orphenadrine	

Acetylsalicylic acid
Allopurinol
Amitriptyline
Amlodipine besilate
Atorvastatin calcium
Baclofen
Bromazepam
Budesonide
Formoterol fumarate
Clobazam
Clotiapine
Codeine phosphate
Meprobamate
Paracetamol
Codeine phosphate
Paracetamol
Promethazine hydrochloride
Estradiol
Norethisterone acetate
Fluoxetine hydrochloride
Furosemide
Hydrochlorothiazide
Lisinopril
Hydrochlorothiazide
Valsartan
Indapamide
Perindopril
Insulin aspart
Insulin degludec
Lacidipine
Lamotrigine
Levetiracetam
Lithium
Olanzapine
Potassium chloride
Prednisolone
Sertraline hydrochloride
Valproic acid sodium

Oxcarbazepine		
Pantoprazole sodium sesquihydrate		
Paracetamol		
Perindopril erbumine		
Phenytoin		
Potassium chloride		
Riboflavin sodium phosphate		
Prednisone		
Quetiapine fumarate		
Risperidone		
Salbutamol		
Sertraline hydrochloride		
Simvastatin		
Tenofovir		
Theophylline		
Thiamine		
Trazodone		
Valproic acid sodium		
Venlafaxine		
Vitamin b complex		
Zuclopenthixol decanoate		

South African National Essential Medicine List
Primary Health Care (PHC), Adult Hospital Level (AHL), Paediatric Hospital Level Medication Review Process
Component:
PHC: Central Nervous System Conditions, AHL: Neurological Disorders, AHL: Paediatric Hospital Level: The Nervous System

SUMMARY

Date: February 2025

Administration of antiseizure medications via nasogastric tube (NGT)

Background

This document provides a summary of the administration of antiepileptic medicines via NGT from the Handbook of Drug Administration via Enteral Feeding Tubes (written on behalf of the British Pharmaceutical Nutrition Group)[3]. Information is also provided from additional literature identified through a non-structured literature search. Summaries are provided for carbamazepine, lamotrigine, levetiracetam, phenytoin and valproate.

Summary

Carbamazepine

- ***Tablets:*** No specific data on enteral tube administration available for tablets.[Error! Bookmark not defined.] Modified release tablets should not be crushed.
- ***Liquid preparations*** *(Interaction of drug and delivery device):* An invitro study[3] found a loss of drug with use of carbamazepine undiluted suspension administered via a polyvinyl nasogastric tube; however, a 50% diluted suspension resulted in no drug loss. [1]
- ***Peak plasma concentration*** occurs up to 12 hours post oral dose with the tablet formulation; the liquid formulation produces higher and earlier peak plasma concentrations which may be associated with an increase in side-effects[1]

Lamotrigine

- ***Tablets:*** No specific data on enteral tube administration.
- ***Dispersible tablets:*** Tablets disintegrate rapidly when placed in 10 mL of water; the resulting dispersion flushes down an 8Fr NG tube without blockage.
- ***Peak plasma concentration:*** Occurs 2.5 hours after oral dosing. [1]

Levetiracetam

- ***Tablets:*** May be crushed and given via enteral feeding tube.
  - Water-soluble (Brand: Keppra®): 1.04g/mL at room temperature.

- 500 mg tablets (only strength tested) disperse in 10 mL of water if shaken for 5 minutes. This forms a milky, even dispersion that flushes down an 8Fr NG tube without blockage.[1]

- ***Oral solution:*** dilute with twice volume of water. [1]
- ***Peak plasma concentration:*** Oral bioavailability is nearly 100%. Peak plasma concentration occurs at 1.3 hours post dose.

- Birbeck et.al: Conducted a clinical trial of enteral levetiracetam for acute seizures in pediatric cerebral malaria[3].
    - » Study evaluated the pharmacokinetic safety and efficacy of enteral levetiracetam versus phenobarbital.
    - » N = 30 comatose children with cerebral malaria patients (all those allocated to levetiracetam received the treatment, only 15 of the 21 patients assigned to phenobarbital received phenobarbital)
        - o Enteral levetiracetam was rapidly absorbed and well tolerated.
        - o The clearance of enteral levetiracetam was lower in patients with higher serum creatinine.
        - o n = 23 enteral levetiracetam vs n = 15/21 phenobarbital patients:
            - No differences for minutes with seizure (Mean (SD): 165 (266) vs 465 (639); p = 0.54).
            - No difference in seizure freedom (19 (83%) vs 16 (76%), p=0.72).
            - No difference in coma duration (mean hours, SD) (35.4 (29.0), n=22 vs 34.6 (27.8), n=16, p=0.91).
            - No difference in neurologic sequelae or death (3 vs 2).
            - No difference in death (1 vs 5).
            - Enteral levetiracetam was considered safer than phenobarbital (p = 0.019).
            - Phenobarbital was discontinued in 3/15 (20%) due to respiratory side effects.
- Shibata et.al.: Early enteral levetiracetam in diazepam-resistant convulsive status epilepticus (SE)[3]
    - » Single center prospective study to evaluate the efficacy and safety of levetiracetam administration through NGT in acute convulsive SE resistant to intravenous diazepam:
    - » 8/9 diazepam-resistant patients (88.9%) vs 11/12 (91.7%) diazepam-responders, the seizures were controlled within 30 minutes after diazepam (P = 1.00).
    - » 3-day seizure freedom rate was equivalent in the two groups (88.9 vs 83.3%, P = 1.00).
    - » Less than 10% of the overall patients had levetiracetam-related mild side-effects (no differences between the two groups).

Phenytoin

- ***Capsules:*** Some can be opened and powder mixed with 10 mL of water (does not initially mix, but if left for 5 minutes and stirred, if forms a fine dispersion that can be flushed down an 8Fr NGT without blockage.
- ***Tablets:*** Difficult to crush due to film coating and do not disperse readily.
- ***Suspension:*** Viscous, thixotropic (less viscous when agitated, and then return to their original state over time) suspension. Recommended to dilute with equal parts water.
- ***Site of absorption:*** Phenytoin is absorbed from the small intestine after oral administration. Peak plasma concentration occurs 2–4 hours and 10–12 hours post oral dosing. [1]

Valproate

- ***Tablets:***
  - Crushable valproate tablets can flush easily down an 8Fr NGT.
  - Enteric coated or modified release tablets cannot be crushed.
- ***Liquid:*** resistant to flushing via 8Fr NGT but mixes with water which reduces resistance. (note: liquid formulation might contain sorbitol).
- Peak plasma concentration occurs 1–2 hours after administration of liquid and immediate-release preparations, and 2–8 hours after enteric coated or modified-release preparations. [1]

Summary Table

Antiepileptic Medicine	Formulation	Notes	Administer via NG Tube
Carbamazepine	Tablets	No specific data. Modified release tablets should not be crushed.	?
	Liquid	(Interaction of drug and delivery device): Loss of drug with use of carbamazepine undiluted suspension, a 50% diluted suspension resulted in no drug loss.	Yes only if diluted
Lamotrigine	Tablets	No specific data on enteral tube administration.	?
	Dispersible tablets	Tablets disintegrate rapidly when placed in 10 mL of water; the resulting dispersion flushes down an 8Fr NG tube without blockage.	Yes
Levetiracetam	Tablets	May be crushed and given via enteral feeding tube.	Yes
	Oral solution	dilute with twice volume of water.	Yes
Phenytoin	Capsules	Some can be opened and powder mixed with 10 mL of water (does not initially mix, but if left for 5 minutes and stirred, if forms a fine dispersion that can be flushed down an 8Fr NGT without blockage.	Yes
	Tablets	Difficult to crush due to film coating. Do not disperse readily.	No
	Suspension	Viscous, thixotropic (less viscous when agitated, and then return to their original state over time) suspension. Recommended to dilute with equal parts water.	Yes
Valproate	Tablets (Crushable)	Crushable valproate tablets can flush easily down an 8Fr NGT.	Yes
	Tablets (Enteric Coated)	Enteric coated or modified release tablets cannot be crushed.	No
	Liquid	Resistant to flushing via 8Fr NGT but mixes with water which reduces resistance.	Yes only if flushed with water

Taken from: White R, Bradnam V. Handbook of Drug Administration via Enteral Feeding Tubes. Pharmaceutical Press. 2007

NEMLC Recommendation: 27 February 2025

NEMLC accepted the proposal to offer levetiracetam via nasogastric tube.