SESLHDMG/129

Medicine Guideline

Subcutaneous phenobarbital (S4D) for refractory terminal agitation and uncontrolled seizures(including staus epilepticus) in the imminently dying patient

Areas where Protocol/Guideline applicable	SESLHD Inpatient settings (including Calvary hospital)
Authorised Prescribers:	Specialist Palliative Care Service involvement essential
Indication for use	1. Refractory terminal agitation **not** responding to first or second line therapy:- • First-line therapy: Midazolam 60 to 200mg in 24hours and/or Haloperidol 10mg in 24hours • Second-line therapy: Levomepromazine to a maximum of 300mg in 24hours. 2. Severe and uncontrolled seizures, including status epilepticus, not responding to benzodiazepines and/or levetiracetam
Clinical condition	Agitation in the last days of life is multifactorial in origin, including complex poorly controlled symptoms, delirium, emotional and existential distress, medication toxicity and metabolic changes. Management includes identifying reversible causes, and use of medications as above.
Proposed Place in Therapy	Third line therapy for refractory agitation. Second or third line therapy for severe uncontrolled seizures.
Contra-indications and precautions	No absolute contraindications if the patient is in terminal phase/last days of life. Caution in: • Porphyria • Hypersensitivity syndrome with carbamazepine, phenytoin or phenobarbital • Allergy or rash with other antiepileptics - may increase risk of rash with phenobarbital or primidone • Respiratory disease - risk of respiratory depression
Important Drug Interactions	Phenobarbital induces various enzymes involved in drug metabolism, and thus has clinically significant interactions with many drugs, including other drugs used in end-of-life care, such as benzodiazepines, opioids, other antiepileptics, paracetamol, and haloperidol. For a full exposition of potential interactions please see UptoDate or Micromedex, or discuss with pharmacy for expert advice.

Dosage (Include dosage adjustment for specific patient groups)	Dose to be determined by consultation with Palliative Care Consultant **Terminal agitation:** **Initial dose**: 200mg stat via **intramuscular (IM)** injection then, titrate by 200mg IM hourly until settled while commencing the syringe driver for maintenance (outlined below) **Subsequent dosing**: 800 mg via continuous subcutaneous infusion (CSCI) over 24 hours. Consider higher starting dose if patient has required multiple IM doses. This can be titrated progressively based on symptom control eg: 800mg to 1200mg to 1600mg to 3200mg via CSCI over 24 hours. (A typical dose is 800 to 1200mg/24 hours but can range from 200mg to 3,800mg / 24 hours). **Uncontrolled seizures / status epilepticus:** **Initial dose**: 200mg stat via intramuscular (IM) injection **Subsequent dosing**: 800 mg via continuous subcutaneous infusion (CSCI) over 24 hours. This can be titrated progressively eg: 800mg- 1200mg – 1600mg - 3200mg via CSCI over 24 hours. Additional PRN/breakthroughs doses of 50 to 200mg hourly via **IM injection** should also be prescribed based on symptom control. Regular dose should be titrated according to the need for breakthrough doses. ***Consider reduced starting doses in the elderly and in renal or hepatic impairment.***
Preparation	Phenobarbital sodium 200mg/1mL vials
Prescribing Instructions	Phenobarbitone must be prescribed on the eMM system. In the absence of eMM systems, the appropriate paper medication chart may be used.
Administration Instructions	**Doses ≤**1600mg/24 hours may be administered via CSCI diluted to 17mL with water for injections (in a 20mL syringe). **Doses >**1600mg would require two syringe drivers. Seek advice from the Palliative Care team.

Diluents	Water for Injection (WFI) for use via syringe driver (doses ≤1600mg) Sodium chloride 0.9% for doses >1600mg via infusion pump
Drug Compatibility	Phenobarbital **should not be mixed in a syringe with any other medication** due to its alkaline pH and lack of robust compatibility data. Administer alone in a separate syringe driver.
Adverse effects	Respiratory depression (high doses), drowsiness, lethargy, ataxia, skin reactions (<3%). Paradoxical excitement, irritability, restlessness/hyperactivity and delirium.
Monitoring requirements Safety Effectiveness (state objective criteria)	Monitor seizure activity and titrate dose accordingly. Monitor closely for infusion site reactions. Minimum 4 hourly site checks as per Subcutaneous Syringe Driver Inpatient Management Form SES130.021.
Management of Complications	If there are signs of irritation at the injection site refer to the attending medical officer immediately.
Practice Points	Must be sufficiently diluted due to the risk of tissue damage/necrosis. Maximum recommended concentration is 20mg/mL (200mg in 10mL). **PRN/Breakthrough doses must be prescribed and administered as IM injection due to high pH and risk of tissue damage/necrosis with bolus subcutaneous injection.**
Basis of Protocol/Guideline:	Palliative Care Formulary online in Medicines Complete, accessed via CIAP. Date accessed 20/02/2025. Therapeutic Guidelines -Palliative Care (eTG) [December 2024] In Therapeutic Guidelines. Melbourne: Therapeutic Guidelines Limited; accessed {20/2/25} via CIAP. Scottish Palliative Care Guidelines – Phenobarbital 2018
Groups consulted in development of this guideline	SESLHD Palliative Care working party. Dr Caitlin Sheehan, Head of Department -Palliative Care St George Hospital Mary Lafferty CNC Palliative Care St George Hospital

SESLHDMG/129

Medicine Guideline

Subcutaneous phenobarbital (S4D) for refractory terminal agitation and uncontrolled seizures(including staus epilepticus) in the imminently dying patient

AUTHORISATION	
Author (Name)	Dr Linda Sheahan
Position	Clinical Stream Director, Palliative and End of Life Care
Department	SESLHD
Position Responsible (for ongoing maintenance of Protocol)	linda.sheahan@health.nsw.gov.au
GOVERNANCE	
Enactment date *Reviewed* (Version 2) *Reviewed* (Version 3)	November 2020 December 2023
Expiry date:	April 2028
Ratification date by SESLHD DTC	5 April 2025
Chairperson, DTC	Stuart Binns, A/Chair SESLHD DTC
Version Number	3.0