Title	**Subcutaneous phenobarbital for refractory terminal agitation and uncontrolled seizures (including status epilepticus) in the imminently dying patient.**
Area where Protocol/Guideline applicable	SESLHD Inpatient settings (including Calvary hospital)
Authorised Prescribers	Specialist Palliative Care Service involvement essential
Indications for use	1. Refractory terminal agitation **not** responding to first or second line therapy: First-line therapy: Midazolam 60 – 200mg in 24hours and/or Haloperidol 10mg in 24hours Second-line therapy: Levomepromazine 200mg in 24hours. 2. Severe and uncontrolled seizures, including status epilepticus, not responding to benzodiazepines and/or levetiracetam
Place in Therapy	Third line therapy for refractory agitation. Second or third line therapy for severe uncontrolled seizures,
Clinical condition	Agitation in the last days of life is multifactorial in origin including complex poorly controlled symptoms, delirium, emotional distress, medication toxicity and metabolic changes. Management includes identifying reversible causes and use of medications as above.
Contraindications 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
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, other antiepileptics, paracetamol, haloperidol.
Dosing	Dose to be determined by consultation with Palliative Care Consultant <u>Terminal agitation:</u> Initial dose: 200mg stat via **intramuscular** (**IM**) injection then,

	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. (A typical dose is 800 – 1200mg/24 hours but can range from 200mg – 3,800mg / 24 hours) <u>Uncontrolled seizures / status epilepticus:</u> 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 50-200mg hourly via **IM injection** should also be prescribed. 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**
Preparations	Phenobarbital sodium 200mg/1mL vials
Administration	**Doses ≤**1600mg/24 hours may be administered via CSCI diluted to 17mL with water for injections (in a 20mL syringe). **Doses >**1600mg should be infused in sodium chloride 0.9% via an infusion pump. 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 & lack of robust compatibility data.
Known Adverse Effects	Respiratory depression (high doses), drowsiness, lethargy, ataxia, skin reactions (<3%). Paradoxical excitement, irritability, restlessness/hyperactivity and delirium
Monitoring requirements	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 injections**

	Administer alone in a separate syringe driver
Basis of Protocol/Guideline (including sources of evidence, references)	Palliative Care Formulary 7th Ed, 2020 p309-313 Therapeutic Guidelines – Palliative Care eTG, July 2018 Dickman A, Schneider J. The syringe driver: continuous subcutaneous in palliative care. Oxford University Press; 2016 Scottish Palliative Care Guidelines – Phenobarbital (Phenobarbitone), 2018
Consultation version 2	SESLHD Palliative Care working party. Dr Caitlin Sheehan, Head of Department -Palliative Care St George Hospital Mary Lafferty CNC Palliative Care St George Hospital

AUTHORISATION	
Author (Name)	Dr Jan Maree Davis
Position	Medical Director, Palliative Care
Department	SESLHD Southern Sector
Department Contact (for ongoing maintenance of Protocol/Guideline)	JanMaree.davis@health.nsw.gov.au
GOVERNANCE	
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Chairperson, SESLHD DTC	Dr John Shephard
Version Number	2
Version 2 changes	Increased doses for Terminal agitation and seizures as per PCF 8th edition 2022