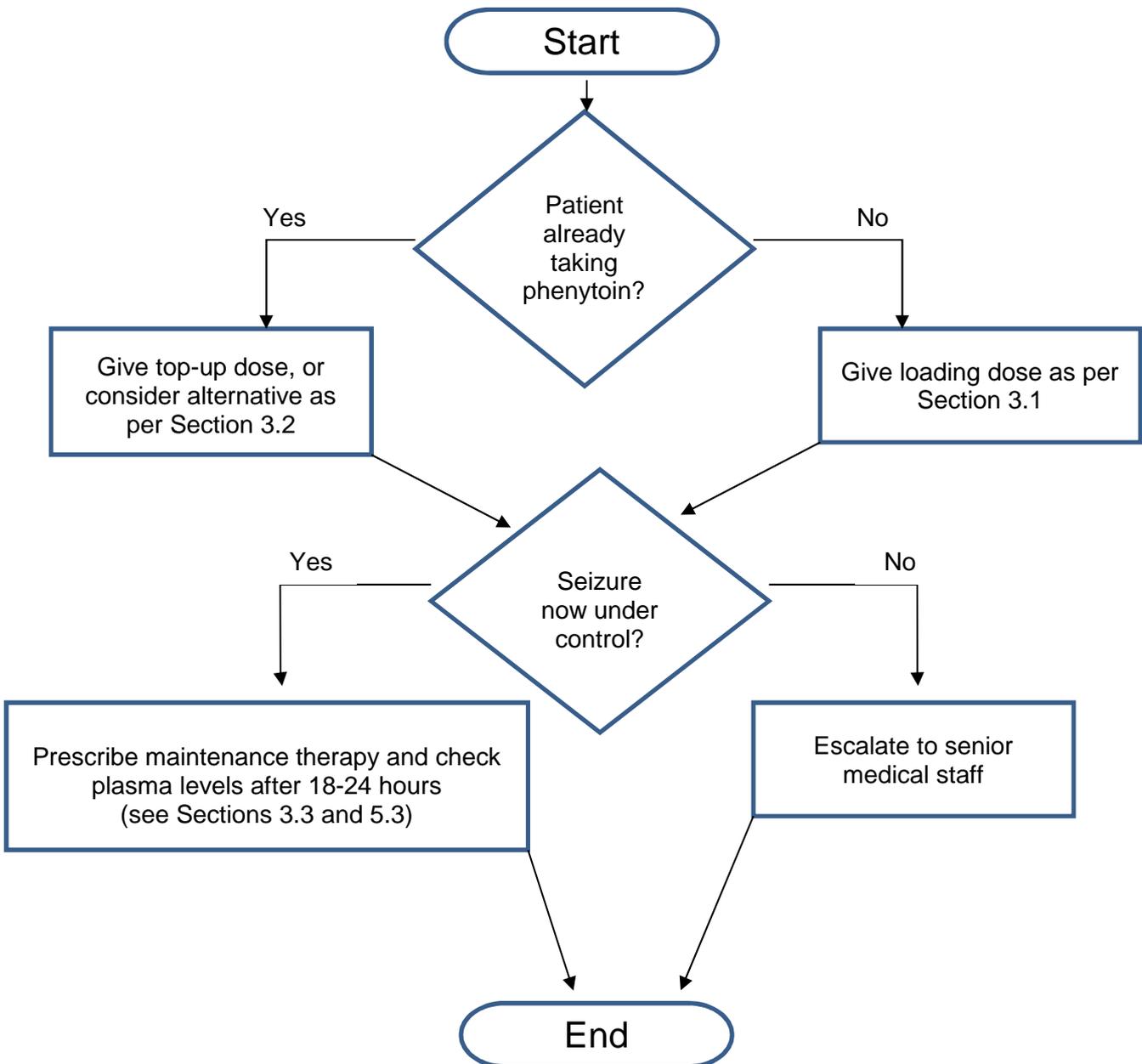
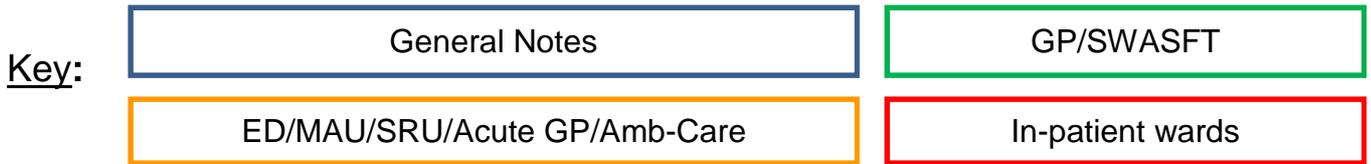


This applies to adult patients only

# CLINICAL GUIDELINE FOR THE USE OF PHENYTOIN IN EPILEPSY



## 1. Aim/Purpose of this Guideline

1.1. To provide clinical staff with guidance relating to the management of phenytoin for status epilepticus and follow-on therapy in adults.

## 2. Background

2.1. A recent Patient Safety Alert highlighted the risk of death and severe harm from error with intravenous phenytoin following 2 recent fatalities. Phenytoin is one of a number of treatments used in the management of status epilepticus, following which it can be used as maintenance treatment. However, the use of phenytoin is not straightforward; it has a narrow therapeutic index and its use in status epilepticus is further complicated by the requirement for a loading dose.

### 2.2. When should phenytoin be used for status epilepticus?

<b>Premonitory stage (pre-hospital)</b>	Diazepam 10–20 mg given rectally, repeated once 15 minutes later if status continues to threaten, or midazolam 10 mg given buccally. If seizures continue, treat as below.
<b>Early status</b>	Lorazepam (intravenous) 0.1 mg/kg (usually a 4 mg bolus, repeated once after 10–20 minutes; rate not critical). Give usual AED medication if already on treatment. For sustained control or if seizures continue, treat as below.
<b>Established status (failed to respond 25 minutes after onset)</b>	Phenytoin infusion - see Section 3.1 for loading doses  If the patient is already taking phenytoin, see Section 3.2  Phenobarbital bolus of 10–15 mg/kg at a rate of 100 mg/minute N.B. this is usually only given on the Critical Care unit due to the risk of respiratory failure, especially if benzodiazepines have been previously administered.
<b>Refractory status</b>	General anaesthesia

Table 1: Emergency AED therapy for convulsive status epilepticus (adapted from NICE)

### 3. Phenytoin dosing

Use the red supplementary drug chart for an IV prescription.

Sample prescription – example 70kg patient:

EPMA Supplementary intravenous therapy prescription sheet										Patient name		
All infusions, infusion fluids, blood and plasma must also be prescribed in EPMA												
Date	Infusion solution	Name and dose of additive	Infusion volume	Duration of infusion	Infusion rate	Proposed start time	Prescriber signature	Infusion bag batch no.	Time actually started	Given by	Time finished	Pharmacy use
										Checked by		
1/4/2014	Sodium Chloride 0.9%	Phenytoin 1250mg	250mL	35 minutes			Doctor (bleep)					

#### 3.1. IV loading dose

For phenytoin-naïve patients, loading doses can be calculated as follows:

Weight (kg)	Dose (mg/mL)
40-49	750mg in 100mL
50-64	1000mg in 100mL
65-78	1250mg in 250mL
78-92	1500mg in 250mL
>92	1750mg in 250mL

Table 2: Banded phenytoin loading doses

#### 3.2. Patients already on phenytoin

3.2.1 If a phenytoin level is known, single 'top-up' doses of 250-750mg for patients already taking phenytoin with sub-therapeutic levels can be calculated using the formula:

$$\text{phenytoin 'top-up' dose [mg]} = (20 - \text{phenytoin level [mg/L]}) \times 0.7 \times \text{weight [kg]}$$

Dose	Body weight			
	50kg	60kg	70kg	80kg
	Concentration increase			
250 mg	7 mg/L	6 mg/L	5 mg/L	4.5 mg/L
500 mg	14 mg/L	12 mg/L	10 mg/L	9 mg/L
750 mg	21 mg/L	18 mg/L	15 mg/L	13.5 mg/L

Table 3 – Increase in phenytoin concentration with 'top-up' doses (adapted from UKMI)

For example, if the patient weighs 70 kg and has a plasma level of 5 mg/L, a single dose of 750 mg will increase the plasma concentration from 5mg/L to 20mg/L ie by 15mg/L.

### 3.2.2 When phenytoin levels are not immediately available:

Phenytoin levels may take up to an hour to be reported and treatment in status epilepticus should not be delayed. If it is not possible to obtain phenytoin levels in a timely manner, options include:

- giving half the recommended loading dose until levels are available
- limiting loading doses to 500mg
- using an alternative drug such as sodium valproate or levetiracetam
- contacting the neurology team

## 4. Administration:

- Before giving, closely inspect the solution for precipitates or discolouration (injection must be clear, but a faint yellow colour is acceptable).
- **Do not dilute in a glucose-containing solution. Do not mix with any other fluids or medicines, as precipitation may occur**
- Administer via a **large gauge cannula** through a **0.2micron filter** into a **large vein**, as phenytoin has a high pH and a high osmolality, making it irritating to veins and causing tissue damage if extravasation occurs. Flush the line with sodium chloride 0.9% before and after administration to avoid local venous irritation.

### 4.1 Loading dose

- Dilute in 100-250mL of sodium chloride 0.9% and give over 35 minutes.

### 4.2 Maintenance and top-up doses

- IV phenytoin can be given undiluted by slow injection (preferred) or in a diluted infusion.
- Inject via a syringe pump at a rate not exceeding 50 mg/min. In elderly patients, or those with pre-existing cardiac disease, give at a maximum of 25 mg/min.
- If dilution is essential, dilute with 50-100mL sodium chloride 0.9% to a final concentration of less than 10 mg/mL and administer via a 0.22-0.5 micron in-line filter.

**Do not dilute with any fluid other than sodium chloride 0.9%.**

**Do not mix with any other drugs.**

**Prepare immediately before administration, and ensure the infusion is completed within 1 hour of preparation.**

For further information, please check [Medusa](#)

### 4.3 Administration via enteral feeding tubes

- Administration via enteral feeding tubes is not generally recommended. Contact Medicines Information for further advice if necessary

## 5. Monitoring:

- Check LFTs and FBC before initiating.
- Continuous ECG and regular blood pressure and respiratory rate monitoring is essential. Reduce rate of administration if bradycardia or hypotension occurs.
- Cardiac resuscitation equipment should be available.
- Inspect injection site regularly for any signs of irritation or inflammation
- Inform medical staff immediately if the following occur:
  - Hypotension (marked drop in BP from patient's baseline)
  - Arrhythmias
  - Respiratory depression
  - **ANY** pain/erythema at Venflon site, especially tracking along arm

## 6. Maintenance dose:

- Start 18 to 24 hours after the loading dose
- IV or PO – start with 100mg TDS or 300mg OD.
- Slow IV injection over 2 minutes or IV infusion using a 0.2micron filter and complete infusion within one hour of preparation
- Doses should be adjusted carefully according to plasma concentrations at increments of **not more than 25-50mg per day**
- Usual maintenance doses range from 200mg to 500mg per day, preferably taken as a single dose at night

100mg phenytoin sodium as injection, tablets or capsules is approximately equal in therapeutic effect to 90mg phenytoin base as suspension (90mg/15ml) or Epanutin Infatabs

## 7. Renal / hepatic impairment:

- 7.1 Dose as in normal renal function. Monitor closely, as protein binding may be decreased, leading to increased free phenytoin.
- 7.2 Dose reductions may be needed in hepatic impairment to avoid toxicity

## 8. Pharmacokinetic considerations:

- 8.1. Phenytoin is a narrow therapeutic drug - there is little difference between a sub-therapeutic, a therapeutic, and a toxic dose. After initial loading, doses should be guided by plasma levels and the larger clinical picture:
- 8.1.1. Therapeutic plasma concentrations tend to reside between 10-20 mg/L, although some patients may be controlled with lower serum levels
  - 8.1.2. Toxicity is generally seen with plasma concentrations >20 mg/L
  - 8.1.3. Nystagmus, ataxia and diminished mental capacity are seen at 30-40 mg/L
  - 8.1.4. Cardiac toxicity may be more related to rapid administration rates, potentially due to transient, high concentrations

8.2. Phenytoin displays capacity-limited metabolism. This means that for a small increase in a therapeutic dose, there can be a large increase in steady state concentrations. Adjustment of phenytoin maintenance doses should be made cautiously, at increments of no more than 25-50mg per day.

### 8.3. Therapeutic drug monitoring

8.3.1. Trough levels should be taken 18-24 hours after loading, and before the first maintenance dose is given.

8.3.2. Steady state usually occurs 7-10 days after initiation of therapy. Monitor maintenance plasma levels 2 weeks after any dose changes, or following the introduction/withdrawal of a potentially interacting drug.

8.3.3. Do not base treatment on plasma levels alone. Efficacy or toxicity should be determined based on the clinical condition of the patient.

8.3.4. Interpretation of phenytoin levels may be altered in hypoalbuminaemia (especially < 32g/L) as well as uraemia and pregnancy. **Contact Pharmacy or Neurology for further advice in these areas.**

## 9. Drug Interactions

9.1. Phenytoin affects and is affected by a large number of drugs. Please see the [BNF](#) for a list of common interactions, and/or ask your ward pharmacist for advice.

9.2. Phenytoin for intravenous use must not be mixed with other drugs.

## 10. Side effects and monitoring

10.1. Serious side-effects include blood dyscrasias and skin disorders such as exfoliative, purpuric or bullous rashes, Lupus erythematosus, Stevens-Johnson syndrome or toxic epidermal necrolysis.

10.2. Other side-effects include: nausea/vomiting, constipation, hepatotoxicity, insomnia, transient nervousness, tremor, paraesthesia, dizziness, headache and anorexia.

10.3. For a full list, please consult the [BNF](#) or relevant SPC

### 10.4. Signs of toxicity

10.4.1. Common signs include nystagmus, diplopia, slurred speech and ataxia. Mental confusion, hyperglycaemia and dyskinesias can also occur.

10.4.2. Overdose may result in hypotension, respiratory depression and coma.

## **10.5. Monitoring requirements**

10.5.1. Check liver function tests (LFTs) and full blood count (FBC) before initiating treatment.

10.5.2. Regular blood test monitoring is not recommended as routine, unless problems are suspected. However, FBC, U&Es, LFTs, vitamin D levels and other tests of bone metabolism are recommended every 2-5 years.

10.5.3. Patients should be counselled on how to recognise signs of blood or skin disorders and monitored for signs of suicidal ideation.

10.5.4. See Section 5.3 for information on therapeutic drug monitoring, and Section 4.1.9 for information on monitoring required during intravenous administration

## **10.6. Withdrawal**

10.6.1. Abrupt withdrawal of phenytoin may precipitate status epilepticus. Doses should be slowly tapered if discontinuation is necessary.

## **11. Other considerations**

11.1. Check allergy status before prescribing phenytoin. Cross-sensitivity has been reported between phenytoin and carbamazepine.

## Monitoring compliance and effectiveness

Element to be monitored	The prescribing and monitoring of phenytoin in epilepsy
Lead	Medications Safety Pharmacist
Tool	An audit tool will be developed to monitor compliance  Datix will be used to identify clinical incidents
Frequency	The policy will be monitored every three years, or sooner as clinical incidents dictate
Reporting arrangements	The audit results will be reported to the Medication Practice Committee (MPC) and the individual areas audited  Clinical incidents on Datix will be reported to the senior nurse/manager in that area and will also be reported to the Medication Safety Group
Acting on recommendations and Lead(s)	The MPC will co-ordinate the actions to the audit results. Actions from incident reports will be at a local level and may also resulting broader actions, co-ordinated by the Medication Safety Group.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned within the time frame specified in the action plan

## 12. Equality and Diversity

12.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the ['Equality, Diversity & Human Rights Policy'](#) or the [Equality and Diversity website](#).

### 12.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

## Appendix 1. Governance Information

<b>Document Title</b>	Clinical guideline for the use of phenytoin in epilepsy			
<b>Date Issued/Approved:</b>	June 2017			
<b>Date Valid From:</b>	June 2017			
<b>Date Valid To:</b>	June 2020			
<b>Directorate / Department responsible (author/owner):</b>	Bronwin Staple, Medicines Information Liam Kelly, Medicines Information Susie Matthews, Medication Safety Jonathan Stewart, Neurology Consultant			
<b>Contact details:</b>	01872 252587			
<b>Brief summary of contents</b>	Dosing and administration instructions for phenytoin in status epilepticus and ongoing maintenance.			
<b>Suggested Keywords:</b>	Phenytoin, Loading Dose, Epilepsy, Status Epilepticus			
<b>Target Audience</b>	RCHT	PCH	CFT	KCCG
	✓			
<b>Executive Director responsible for Policy:</b>	Medical Director			
<b>Date revised:</b>	N/A			
<b>This document replaces (exact title of previous version):</b>	N/A			
<b>Approval route (names of committees)/consultation:</b>	Medication Practice Committee, Neurology			
<b>Divisional Manager confirming approval processes</b>	<i>Head of relevant Division</i>			
<b>Name and Post Title of additional signatories</b>	Not required			
<b>Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings</b>	{Original Copy Signed}			
	Name:			
<b>Signature of Executive Director giving approval</b>	{Original Copy Signed}			
<b>Publication Location (refer to Policy on Policies – Approvals and</b>	Internet & Intranet		Intranet Only	✓

<b>Ratification):</b>				
<b>Document Library Folder/Sub Folder</b>	Clinical / Pharmacy			
<b>Links to key external standards</b>	None			
<b>Related Documents:</b>	<p>NHS Improvement (2016), Patient safety alert - Risk of death and severe harm from error with injectable phenytoin.</p> <p>NICE (2012), CG137 - Epilepsies: diagnosis and management.</p> <p>UKMI (2016), Q&amp;A 444.1 - How can we minimise the risks to patients when using intravenous phenytoin in status epilepticus (SE)?</p>			
<b>Training Need Identified?</b>	No			

### Version Control Table

<b>Date</b>	<b>Version No</b>	<b>Summary of Changes</b>	<b>Changes Made by (Name and Job Title)</b>
February 2017	V1.0	Initial Issue	Bronwin Staple Lead Pharmacist Medicines Information

**All or part of this document can be released under the Freedom of Information Act 2000**

**This document is to be retained for 10 years from the date of expiry.**

**This document is only valid on the day of printing**

### **Controlled Document**

This document has been created following the Royal Cornwall Hospitals NHS Trust Policy on Document Production. It should not be altered in any way without the express permission of the author or their Line Manager.

## Appendix 2. Initial Equality Impact Assessment Form

Name of the strategy / policy / proposal / service function to be assessed (hereafter referred to as <i>policy</i> ) (Provide brief description): Clinical guideline for the use of phenytoin in epilepsy	
Directorate and service area All clinical areas:	Is this a new or existing Policy? New policy
Name of individual completing assessment: Liam Kelly	Telephone: 01872 252587
1. Policy Aim* Who is the strategy / policy / proposal / service function aimed at?	To provide guidance on the dosing and administration of phenytoin in status epilepticus
2. Policy Objectives*	To ensure safe prescribing and use of phenytoin
3. Policy – intended Outcomes*	Use of phenytoin complies with the guidance set out in this document
4. *How will you measure the outcome?	Ongoing audit
5. Who is intended to benefit from the policy?	Patients receiving phenytoin
6a) Is consultation required with the workforce, equality groups, local interest groups etc. around this policy?  b) If yes, have these *groups been consulted?  C). Please list any groups who have been consulted about this procedure.	No   Medications Safety Group, Medicines Information, Neurology

<b>7. The Impact</b>			
Please complete the following table.			
Are there concerns that the policy <b>could</b> have differential impact on:			
Equality Strands:	Yes	No	Rationale for Assessment / Existing Evidence
<b>Age</b>		✓	Policy for all patients
<b>Sex</b> (male, female, trans-gender / gender reassignment)		✓	Policy for all patients
<b>Race / Ethnic communities /groups</b>		✓	Policy for all patients

<b>Disability -</b> Learning disability, physical disability, sensory impairment and mental health problems		✓	Policy for all patients
<b>Religion / other beliefs</b>		✓	Policy for all patients
<b>Marriage and civil partnership</b>		✓	Policy for all patients
<b>Pregnancy and maternity</b>		✓	Policy for all patients
<b>Sexual Orientation,</b> Bisexual, Gay, heterosexual, Lesbian		✓	Policy for all patients
<p>You will need to continue to a full Equality Impact Assessment if the following have been highlighted:</p> <ul style="list-style-type: none"> <li>• You have ticked “Yes” in any column above and</li> <li>• No consultation or evidence of there being consultation- this <u>excludes</u> any <i>policies</i> which have been identified as not requiring consultation. <b>or</b></li> <li>• Major service redesign or development</li> </ul>			
8. Please indicate if a full equality analysis is recommended.		<b>Yes</b>	<b>No</b> ✓
9. If you are not recommending a Full Impact assessment please explain why.			
Policy for all patients			
Signature of policy developer / lead manager / director		Date of completion and submission February 2017	
Names and signatures of members carrying out the Screening Assessment	1. Liam Kelly 2. Susie Matthews 3. Jonathan Stewart		

**Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead,**  
c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa,  
Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed \_\_\_\_\_

Date \_\_\_\_\_