



**NHS Tayside**

**Phenytoin Prescribing and Monitoring  
Guideline in adults**

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**Review Group:** Neurology Clinical  
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**Review Date:** June 2026

**Last Update:** June 2022

**Document No:**

**Issue No:** 4.0.

**UNCONTROLLED WHEN PRINTED**

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## 1. Phenytoin Overview

Phenytoin is an antiepileptic agent which is an effective, second line treatment for status epilepticus (see NHS Tayside Protocol for the management of in-patient status epilepticus in adults <sup>1</sup>). It has a narrow therapeutic index and the relationship between dose and serum phenytoin concentration is non-linear. A small change in dose can result in a large increase in serum concentration and can result in acute toxicity. By the same principle, missing several doses or a small change in drug absorption can cause a significant change in serum phenytoin concentration. Therapeutic drug monitoring can aid dosage adjustment (see Section 3 for further advice).

Phenytoin preparations are not bioequivalent and care must be taken when switching between formulations and administration routes. Therapeutic monitoring may be required when switching formulations (see Section 4 for further guidance).

### Indications<sup>1,2</sup>

- Status Epilepticus
- Uncontrolled Seizures
- Treatment of Epilepsy (except Absence Seizures)
- Neuralgias (not covered in this guideline)

### Contraindications<sup>2</sup>

- Sinus Bradycardia
- Sino-atrial block
- Second and third degree heart block
- Stokes-Adams syndrome
- Acute porphyria
- Avoid in Han Chinese or Thai with HLA-B\* 1502 allele unless essential (increased risk of Stevens-Johnson syndrome)<sup>1</sup>
- Within first three months after myocardial infarction

### Caution<sup>1</sup>

- Cross sensitivity reported with carbamazepine
- Hepatic impairment (reduce dose to avoid toxicity)
- Enteral feeding (interrupt feeding for 2 hours before and after dose)

### Adverse Effects<sup>1,2</sup>

- Nystagmus, ataxia, slurred speech
- Drowsiness and confusion
- Hypotension, Prolonged QT interval and arrhythmias (rapid IV admin)
- Gingival hyperplasia (long term)
- Rashes (discontinue)
- Blood Disorders (Aplastic anaemia, Agranulocytosis, Thrombocytopenia, Megaloblastic anaemia)
- Folate Deficiency
- Antiepileptic hypersensitivity syndrome
- Hirsutism and coarsening of facial appearance
- Leucopenia, ( if severe, progressive, or associated with clinical symptoms – withdraw)
- Osteoporosis and bone fractures (long term)

## 2. Intravenous Loading Dose in Status Epilepticus

If the patient is **not currently on phenytoin** then load patient with Phenytoin Sodium IV

**18mg per kg (max dose 1800mg)**

Intramuscular injection **should not** be used status for epilepticus.

### *Intravenous Loading Dose Administration Guidance*

- Administer, using an in-line filter (0.22 – 0.50 microns), directly into a large vein via syringe pump through a large-gauge needle or via intravenous catheter<sup>1,4</sup>
- Administer slowly undiluted<sup>3</sup>. Give over 30- 40 minutes (maximum rate of 50mg (1mL)/minute). In the elderly or those with pre-existing cardiac disease give over 60-80 minutes (maximum rate of 25mg/minute)<sup>1,2,3</sup>
- If dilution required before administration, dilute to 50-100mL with sodium chloride 0.9%. The final concentration should not exceed 10mg per 1mL<sup>4</sup>. Administration should commence immediately after the mixture has been prepared and must be completed within one hour.
- Continuous monitoring of the electrocardiogram, respiratory function and blood pressure is essential when loading patient with phenytoin<sup>1,2,3,4</sup>
- To avoid local venous irritation each injection or infusion should be preceded and followed by an injection of 0.9% saline through the same needle or catheter<sup>1,3,4</sup>

**See section 5 for advice on taking levels following loading doses.**

### 3. Top Up Dose for Patients in Status Epilepticus but already on Phenytoin

If the patient is already on phenytoin and status epilepticus occurs a 'top-up' loading dose may help patient reach therapeutic levels. A phenytoin level should be taken to establish the current plasma concentration and can be used to calculate the required 'top-up' loading dose.

**Top-Up Phenytoin = (20 – (measured concentration (mg/L)) x 0.7 x weight (kg)  
Sodium Dose**

Table 1 describes how much the serum concentration will increase with a 'top-up' loading dose. A concentration of 20mg/L should be aimed for. For example, in a 70kg patient with a measured phenytoin concentration of 5mg/L could be given a single top-up dose of 750mg to achieve a concentration of 20mg/L.

**Table 1: Expected Increase in Phenytoin Concentration with “Once Only” Top-Up Dosing**

Dose	Patient's weight	Increase in Concentration			
		50 kg	60 kg	70 kg	80 kg
200mg		6 mg/L	5 mg/L	4 mg/L	3.5 mg/L
250 mg		7 mg/L	6 mg/L	5 mg/L	4.5 mg/L
300mg		8.5 mg/L	7 mg/L	6 mg/L	5 mg/L
400 mg		11.5 mg/L	9.5 mg/L	8 mg/L	7 mg/L
500 mg		14 mg/L	12 mg/L	10 mg/L	9 mg/L
600 mg		17 mg/L	14 mg/L	12 mg/L	11 mg/L
750 mg		21 mg/L	18 mg/L	15 mg/L	13.5 mg/L

*N.B. Please remember that in patients with hypoalbuminaemia measured concentration must be corrected before using above calculation.*

**See section 5 for advice on taking levels following top-up.**

#### 4. Maintenance Phenytoin Therapy

Maintenance intravenous phenytoin therapy of 3-5mg/kg/day in three divided doses. The usual starting dose is 100mg IV TDS or 300mg ONCE daily if oral route is available and should be commenced 12 – 24 hours after loading dose. Doses should be adjusted gradually according to plasma-phenytoin concentrations.

When appropriate convert to nasogastric or oral administration. When converting patients from IV to oral maintenance the dose is kept the same however it is usually switched to once daily at night (e.g. 100mg TDS IV = 300mg nocte).

The only exception to the above is when converting the patient from IV to phenytoin suspension or when converting the patient from capsules to suspension. Suspension is formulated as phenytoin base while capsules and injection are formulated as phenytoin sodium. Therefore dosage adjustment is required due to the difference in bioavailability.

**100mg phenytoin sodium (capsules/injection) = 90 mg phenytoin base<sup>9,10</sup>  
(suspension)**

Suspension (90mg/5mL) is available for NG administration or those with swallowing problems. Dose conversion is however required and interaction with other medications and NG feed can occur. Contact clinical pharmacist for assistance when using suspension and/or NG administration.

##### *Phenytoin Administration via Enteral Feeding Tubes*

- Absorption can be poor so consider keeping critically ill patients on intravenous therapy until stable or monitor levels closely<sup>9</sup>.
- Phenytoin suspension is very viscous and hyperosmolar therefore dilution with equal amounts of water is recommended.
- Phenytoin interacts with feed therefore feed must be stopped for 2 hours before and after giving phenytoin via enteral feeding tubes. Flush the feeding tubes with saline before and after phenytoin administration. In these situations it is recommended to prescribe phenytoin as a single daily dose<sup>9,10</sup>.

**See section 5 for advice on therapeutic drug monitoring for patients on maintenance therapy.**

## 5. Therapeutic Drug Monitoring

Phenytoin has a narrow therapeutic index and has non-linear kinetics. This can result in difficulties in dose adjustment and interpretation of levels. **A small change in dosing can result in a large change in blood levels.**

Drug monitoring in patients with epilepsy should NOT be routinely performed unless to assess adherence or suspected toxicity or after adjustment of phenytoin dose <sup>2,5</sup>.

**Target Concentration = 10-20 milligrams per litre** <sup>1,2</sup>

Some cases of tonic-clonic seizures can be controlled with lower concentrations <sup>1,2</sup>.

The patient's clinical status is more important than concentration measurements and this should always be considered when considering dosage adjustment. Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity.

### 5.1 Signs and Symptoms of Toxicity

- Ataxia, Slurred speech (very typical presentation for patients with elevated levels (>30mg/L))
- Confusion
- Hallucinations
- Tremor
- Irritability or agitation
- Encephalopathy
- Nystagmus ( usually levels > 20mg/L but can occur at lower levels)
- Diplopia

Seizures and death can occur as a result of toxicity but this is usually at concentrations > 50mg/L.

### 5.2 Monitoring following Loading/Top-Up Dose

A level can be taken 2-4 hours following an IV loading or top-up dose (12-24 hours for oral doses) and levels should then be monitored **every 24 hours** until control is achieved and concentration has stabilised. It is important to take the sample at the same time every day to allow for true comparison and whether concentration is stable, increasing or decreasing in response to dosage regimen <sup>7,8</sup>.

### 5.3 Monitoring during maintenance therapy

A trough level (i.e. sample prior to next dose) should be taken 3-5 days after commencing maintenance therapy or after a change in dose. A second sample should then be taken after a further 5-10 days as further accumulation may occur <sup>7,8</sup>. If trough levels are not possible then samples should be taken at a similar time of day for comparison.

As previously mentioned phenytoin concentrations do not increase in proportion with dosing. Therefore increasing the dose by more than 25-50mg per day can result in toxicity. The following table provides a rough guide to adjusting the dosing in accordance with measured concentrations however discussion with your clinical pharmacist is strongly encouraged <sup>7,8</sup>.

**Table 2 Phenytoin Maintenance dose adjustment**

Measured concentration	Current dose	Maximum dose increase
<5mg/L	<4.5mg/kg/day 4.5-6mg/kg/day	100mg
5-10mg/L	4.5-6mg/kg/day >6mg/kg/day	50mg
10-20mg/L	-	25mg
>20mg/L	Withhold dose and check levels daily until target concentration achieved (10-20mg/L). New maintenance dose recalculated.	

Phenytoin capsules are available in the following strengths- 25mg, 50mg, 100mg

**Maintenance dose change (small increments only e.g. 25-50mg)** 35 days after dose change then re-analyse 5-10 days later as further accumulation may occur.

Interpretation of concentration measurements is altered in:

- Hypoalbuminaemia (<35g/L)
- Uraemia
- Pregnancy

#### 5.4 Correction of phenytoin levels in hypoalbuminaemia

Phenytoin is highly protein bound and where protein binding is reduced, as in hypoalbuminaemia, free phenytoin concentration levels will be increased accordingly. Therefore a patient with low albumin (<35g/L) may have a therapeutic level of free phenytoin but an overall low phenytoin level. It is **vital** levels are **corrected** for **albumin** before interpretation in patients with low albumin.

It is recommended to contact pharmacy (ward pharmacist or on-call pharmacist) for advice on correcting the level however the following equation can be used:

$$\text{Corrected Phenytoin Level (mg/L)} = \frac{\text{reported level (mg/L)}}{(0.9 \times \text{serum albumin (g/L)} / 42) + 0.1}$$



## 6. Other Monitoring Requirements

Liver damage and haemopoietic disorders have been associated with phenytoin therefore baseline liver function tests and full blood count should be taken when commencing phenytoin treatment. These should be repeated monthly for the first three months of treatment and six monthly thereafter<sup>2</sup>.

### Skin reactions

Phenytoin can cause rare serious skin reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis<sup>2</sup>. Although these can occur without warning patients should be counselled to report and monitored for rashes, blisters, fever and other signs of hypersensitivity. If rash occurs treatment should be discontinued. If the rash is mild phenytoin can be resumed once the rash has completely resolved. If the rash was to reoccur manufacturer's advice is that further phenytoin therapy is contraindicated.

### Significant Drug Interactions<sup>1,2,6</sup>

Phenytoin is a liver enzyme inducer and therefore has many interactions with other drugs metabolised by this route. This can result in effects on phenytoin levels and interacting drug levels. Consult the BNF Appendix 1 for the full list of drug interactions with phenytoin.

Phenytoin interacts with a number of antiepileptic drugs:

Cenobamate can increase phenytoin levels and it is recommended to take baseline phenytoin levels followed by 4 weekly blood levels until dose is titrated.

Carbamazepine, phenobarbital, valproic acid, sodium valproate can either increase or decrease phenytoin levels.

Lamotrigine, valproic acid, topiramate, zonisamide and levetiracetam can all have their effect reduced by phenytoin.

Please check interactions in the BNF and/or with pharmacy for patients on multiple drug therapies. There is a risk of treatment failure with several interacting medications.

**Table 3 Examples of significant interactions**

Drug	Nature of Interaction
Amiodarone	Increased phenytoin concentrations (metabolism of phenytoin inhibited by amiodarone)
Ciclosporin	Phenytoin induces metabolism of ciclosporin (reduced concentration of ciclosporin)
Aripiprazole	Phenytoin possibly reduces plasma concentration of aripiprazole and an increased dose of aripiprazole may be required
Antiretrovirals	Plasma concentration of boceprevir possibly reduced by phenytoin – manufacturer advised avoiding concomitant use
Caspofungin	Phenytoin reduces plasma concentration of caspofungin – consider increasing caspofungin dose
Corticosteroids	Phenytoin accelerates metabolism of corticosteroids (reduced effect, Prednisolone most affected, hydrocortisone less so)
Digoxin	Phenytoin possibly reduces digoxin levels

Diltiazem	Plasma concentration of phenytoin increased by diltiazem and effect of diltiazem also reduced
Doxycycline	Phenytoin accelerates doxycycline metabolism and levels may be reduced below MIC
Dronedarone, Eplerenone	Phenytoin reduces concentration of these drugs - avoid concomitant use
Fluconazole	Plasma concentration of phenytoin increased by fluconazole (consider reducing dose of phenytoin)
Itraconazole	Phenytoin reduces plasma concentration of itraconazole (avoid concomitant use)
Ketoconazole, Posaconazole	Phenytoin reduces plasma concentration of these drugs
Miconazole	Increases anticonvulsant effects of phenytoin by increasing concentrations of phenytoin
Rifampicin	Phenytoin metabolism accelerated by rifampicin – reduced plasma concentrations of phenytoin
Sucralfate	Reduced absorption of phenytoin
Tacrolimus	Phenytoin may reduce levels of tacrolimus, phenytoin levels may be increased.
Theophylline	Plasma concentrations of both drugs increased when given concomitantly
Trimethoprim / Cotrimoxazole	Phenytoin concentrations increased, also increased antifolate effect
Voriconazole	Phenytoin plasma concentration increased by voriconazole and phenytoin reduces plasma concentrations of voriconazole (increase dose of voriconazole and monitor of phenytoin toxicity)
Warfarin	Phenytoin accelerates metabolism of warfarin (effect of warfarin may be reduced, but increased effect also reported)

Women of child-bearing potential who take phenytoin should be given contraceptive advice. Phenytoin can reduce the efficacy of hormonal contraceptives and the efficacy of phenytoin may be affected by hormonal contraceptives.

## 7. References

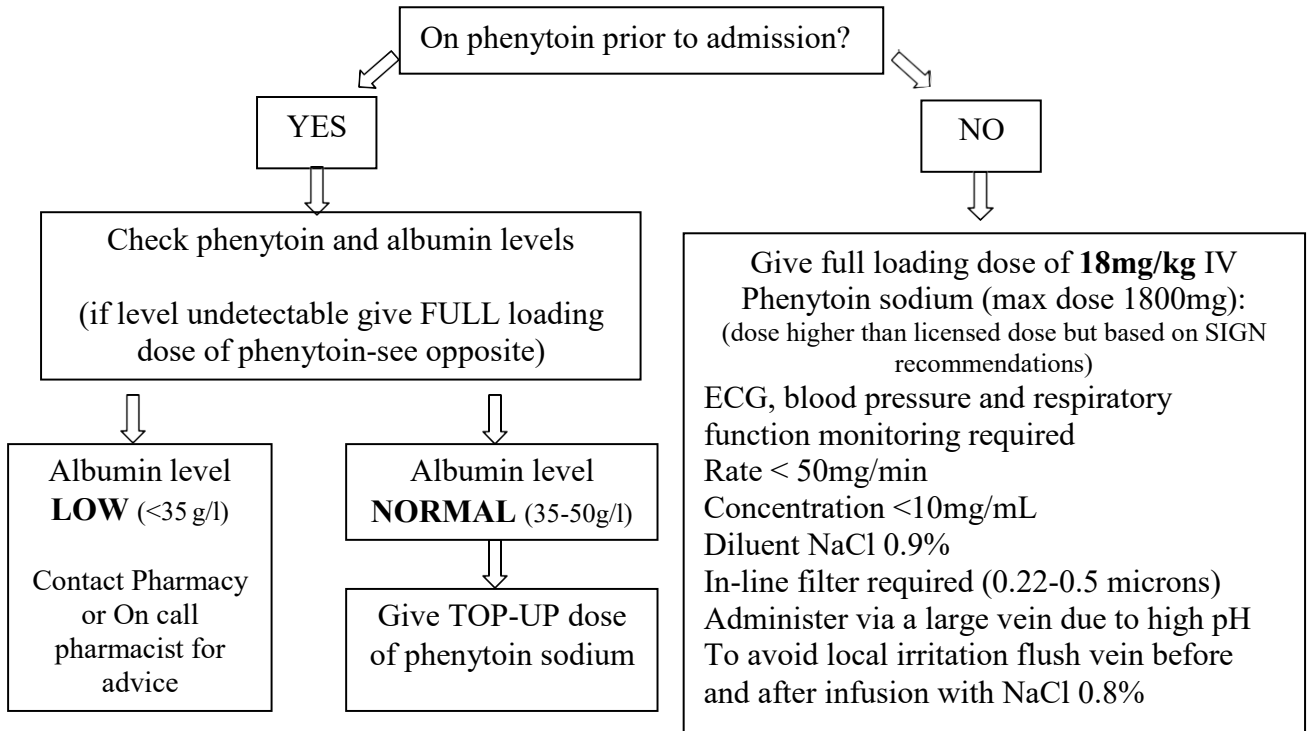
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## APPENDIX 1 SUMMARY OF PRESCRIBING AND MONITORING OF PHENYTOIN

### PHENYTOIN LOADING DOSES

For STATUS EPILEPTICUS or UNCONTROLLED EPILEPSY

Use IV route if STATUS EPILEPTICUS or ORAL ROUTE COMPROMISED



### PHENYTOIN MAINTENANCE DOSES (IV or ORAL)

Give **3-5mg/kg/day** phenytoin sodium  
(Start 12-24 hours after loading dose if given)

<u>Signs of Phenytoin Toxicity</u>		
Drowsiness	Confusion	Slurred speech
Ataxia	Nausea	Nystagmus
Mental Changes	Hyperglycaemia	Coma



