Parenteral phenobarbital

1. **Summary statement of the proposal for inclusion, change or deletion**

Parenteral phenobarbital is proposed for inclusion in the WHO Model List of Essential Medicines for the treatment of status epilepticus in adults and children. Parenteral phenobarbital is widely used in developed countries for this indication, and it is particularly recommended for use in resource-poor countries.

Parenteral phenobarbital is highly effective at controlling epileptic seizures. It is safe and cheap, can be given by slow intravenous push or via the intramuscular route and boluses can be repeated. It is recommended for the treatment of status epilepticus, which is life threatening in not promptly and properly treated.

2. **Name of the focal point in WHO supporting the application:**

Dr Tarun Dua, Management of Mental and Brain Disorders (MBD), Noncommunicable Diseases and Mental Health (NMH)

Dr Martin Weber, Country Implementation Support (CIS), Family and Community Health (FCH)

3. **Name of the organisation consulted and/or supporting the application:**

Dr Matthew Walker, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom

Dr J. Wilmshurst, Head of Paediatric Neurology, Red Cross Children’s Hospital, University of Cape Town, South Africa

4. **International Non-proprietary name:**

Phenobarbital

5. **Formulation proposed for inclusion:**

Phenobarbital Sodium BP 200 mg/mL
6. **International Availability**

Cardinal Health, Martindale Products (Martindale Pharmaceuticals Ltd and Aurum Pharmaceuticals Ltd, Hubert Road, Brentwood, Essex CM14 4LZ) manufacture parenteral Phenobarbital in the United Kingdom. It is available in 1ml ampoules containing 15mg/ml, 30mg/ml, 60mg/ml and 200mg/ml.

According to the WHO Regional Office for Africa (2002) ampoules of phenobarbital (100mg/ml) are produced by the International Dispensary Association. The Médecins sans Frontières (MSF) Medical catalogue lists Phenobarbital sodium as supplied by MSF-Supply and Logistique (200mg/ml), and by MSF-Holland 100mg/ml).

7. **Listing Type required**

Listing is requested as an individual medicine and formulation (parenteral)

8. **Information supporting the public health relevance**

8a. **Epidemiology of status epilepticus**

Status epilepticus is a medical and neurological emergency consisting of continuous seizure activity lasting at least 30 minutes, or two or more seizures without full recovery of consciousness between seizures.

The annual incidence of status epilepticus in Europe is estimated as between 10^3 and 17^4 per 100,000 people, and in America as between 18^3 and 41^6 per 100,000 people. The incidence is thought to be higher in resource-poor countries, although evidence for this is limited. A study conducted between 2001 and 2004 in a hospital in Queensland, Australia, which provides the only specialist neurological services for the region, looked at the patterns of epilepsy in Indigenous and non-Indigenous people presenting to hospital. The health status of the Indigenous population is thought to be typical of that in resource-poor countries. Of those admitted in status epilepticus 44% were Indigenous, compared with 13% Indigenous in the population. The difference was more pronounced in the adults presenting with status epilepticus of whom 53% were Indigenous. A prospective study conducted in Richmond, USA, around 1990, found the annual incident rate to be 20/100,000 in whites, and 57/100,000 in non-whites, but it is difficult to extrapolate this to the rates which would be expected in different countries. There seem to be no studies of the incidence of status epilepticus in resource-poor countries.

The incidence of status epilepticus varies with age, having a bimodal distribution with peaks in early childhood and in the elderly.
Not all people presenting in status epilepticus have a history of epilepsy. Indeed, studies of people in status have shown a previous history of epilepsy in 68% (children 0 to 12 years in Saudi Arabia\textsuperscript{9}), 57% (patients 12 years and over in Hong Kong\textsuperscript{10}), 50% (German adults\textsuperscript{4}), 47% (children up to ten years in India\textsuperscript{11}), 42% (USA, all ages\textsuperscript{9}) and 27% (children in Finland – almost one third had an episode of either febrile or acute symptomatic status epilepticus prior to the onset of epilepsy\textsuperscript{12}).

People with status epilepticus have a high risk of dying, particularly if this is not adequately and urgently treated. One study showed the mortality rate to be 31% in white people with status epilepticus but only 17% in non-white people.\textsuperscript{6} Other studies have shown the mortality to be lowest in children (short-term mortality approximately three to nine percent, long-term mortality in short-term survivors seven percent) and highest in the elderly (short-term mortality 22 to 38%, long-term mortality 82%).\textsuperscript{13} A study conducted in the 1980s set out to find predictors of mortality in adults with status epilepticus.\textsuperscript{14} Overall mortality was 23%, although only two percent died during the status. Those with prolonged status (an hour or more) had a one-month mortality rate of 32% whereas those with status lasting 30 to 59 minutes had one-month mortality of three percent. Mortality increased with increasing age, and non-black people had a higher mortality rate (31%) than black people (19%). Those with status probably alcohol related, or due to AED discontinuation had low mortality rates, while those with anoxia or haemorrhage had high mortality rates. The Saudi Arabian study, looking at 47 children with status epilepticus (59 episodes) found that in only 18 (31%) episodes was appropriate AED treatment initiated. In many cases there was delay in administration of second- or third-line drugs, or delayed treatment of underlying metabolic disturbances.\textsuperscript{9} The Hong Kong study found delay in treatment in 29%, and found that poor outcome (defined as death or functional deterioration) was predicted by increased age, status due to cerebrovascular disease, CNS infection and delay in treatment.\textsuperscript{16} In a retrospective study from India nine of 30 children admitted to the paediatric intensive care unit with status epilepticus died either during seizure activity or before discharge from hospital. The risk of death was increased in those with seizure activity for more than 45 minutes and septic shock.\textsuperscript{11} A study of status epilepticus in 184 subjects with a first non febrile episode of status in Rochester, Minnesota, found case-fatality at 30 days to be 21%.\textsuperscript{15} Most deaths occurred in the group with acute symptomatic aetiology, in whom the case fatality rate was 34% (mostly due to cerebrovascular disease or hypoxic insults). Most deaths occurred in those aged over 65 years. In this study neither seizure type nor duration of status affected the short-term mortality rate. A retrospective study of children in Pakistan found the mortality to be 25%.\textsuperscript{16} In this small study mortality was higher in those under one year, those with abnormal imaging and those with longer duration of status.
8b. **Assessment of current use of parenteral phenobarbital**

Parenteral phenobarbital is included as treatment for status epilepticus in the WHO publication 'Epilepsy: a manual for physicians', recommended in the Advance Paediatric Life Support guidelines, and listed in the Handbook of Paediatrics for developing countries (Oxford Press 2004). It is included in the algorithm for Antiepileptic Drug therapy for status epilepticus in a review article on status epilepticus published in 1998\(^1\).

Parenteral phenobarbital is frequently used to control status epilepticus in resource-poor countries. Phenytoin, the main alternative to phenobarbital in most algorithms, can cause serious skin reactions at the injection site. It should be administered slowly through a large vein, and cardiac monitoring is required (which is frequently not available in resource-poor countries)\(^2\). The infusion is much slower than that of phenobarbital, increasing the risk of refractory status epilepticus, and potential subsequent brain damage. The drug should not be repeated although if needed the second dose should be lower. The prodrug of phenytoin, fosphenytoin, whilst reducing many of the complications of phenytoin treatment, is significantly more expensive. Phenobarbital is faster and easier to administer and as effective as a combination of benzodiazepines and phenytoin \(^3\).

If, as is frequently the case and is recommended, benzodiazepines have been used as first line treatment for status epilepticus, there is an increased risk of respiratory depression if further benzodiazepines are used \(^4\).

No specific diagnostic or treatment facilities or skills are required when using phenobarbital, other than the normal monitoring required of a sick patient for the complications of respiratory depression and hypotension.

The impact of not having parenteral phenobarbital for the treatment of status epilepticus would be increased cardiac complications, lack of early seizure control, prolonged seizures resulting in brain damage and systemic complications. Increased numbers of patients will require artificial ventilation in centres without facilities, and centres with facilities will be unable to cope with the load of ventilated patients due to lack of safe transport systems and bed space.

8c. **Target population**

Parenteral phenobarbital is indicated as second line treatment for status epilepticus refractory to initial treatment with benzodiazepines in both children and adults.
9. **Treatment details**

In adults a loading dose of 20mg/Kg is infused at 50 to 75 mg/min, followed by a maintenance dose of two to four mg/Kg four times daily.\(^{20}\) The loading dose can be followed, if necessary, by a further five to ten mg/Kg \(^{17}\). The British National Formulary suggests an intravenous dose (diluted 1 in 10 with water for injections) of 10mg/kg at a rate of not more than 100mg/minute.\(^{21}\) It has a half-life of 90 hours (70 hours in children), and carries a risk of respiratory depression, particularly if given after benzodiazepines \(^{20}\).

In children phenobarbital can be administered by slow intravenous injection, or even intramuscularly. The dose recommended by Wilmshurst is 20mg/Kg\(^{18}\).

Parenteral phenobarbital is listed in the MSF Essential drugs list for prescription under medical supervision for status epilepticus \(^{22}\). The MSF recommendation is that it be given diluted (1ml in 10ml water for injection) to adults at 10 to 15mg/Kg by slow IV injection at a maximum rate of 100mg/minute, and to children at 15 to 20mg/Kg by slow IV injection. MSF recommends that diazepam rectally or by slow IV injection be given first, followed by phenobarbital by slow IV injection \(^{22}\).

10. **Summary of comparative effectiveness in a variety of clinical settings:**

10a. **Identification of clinical evidence**

A Medline search was undertaken, using the terms ‘status epilepticus and incidence’ and ‘status epilepticus and treatment and phenobarb*’. Additionally reference lists of publications thus located were searched.

10b. **Summary of available data**

Six studies were found providing evidence for effectiveness of parenteral phenobarbital.

A Cochrane Review published in 2005 found only two randomised controlled studies including phenobarbital and using a truly random or quasi-random allocation of treatment suitable for a meta-analysis \(^{23}\). These were the studies by Treiman (1998)\(^{24}\) and Shaner (1988)\(^{19}\).

Treiman et al conducted a randomised, double-blind multi-centre trial of four intravenous regimens; lorazepam, phenobarbital, diazepam followed by phenytoin, and phenytoin. Of 384 adults with a verified diagnosis of overt status epilepticus, 97 were randomised to lorazepam, 91 to phenobarbital, 95 to diazepam and phenytoin and 101 to phenytoin alone. Overall there was a
significant difference in the percentage of patients whose seizures stopped within 20 minutes of the infusion starting (chi squared = 9.6, df = 3, p = 0.02). Whilst lorazepam was the most successful in stopping seizures, it was not significantly more successful than phenobarbital (relative risk 0.84 [95% CI 0.58 to 1.21]). Phenobarbital was marginally, but non-significantly, more successful in stopping seizures than diazepam and phenytoin (relative risk for diazepam/phenytoin 1.06 [95% CI 0.76 to 1.47]), it was significantly more successful than phenytoin alone (relative risk for phenytoin 1.35 [95% CI 1.004 to 1.82]).

Shaner et al conducted a randomised, non-blinded study to compare intravenous diazepam and phenytoin with intravenous phenobarbital in patients over 15 years old with status epilepticus. Data from 36 episodes of status epilepticus (18 on each regime) in 35 patients were used. There was a non-significant difference in the median cumulative convulsing time favouring phenobarbital (5 minutes vs 9 minutes, p < 0.06) and a non-significant difference in response latency (the interval from initiation of medication until the end of the last convulsive episode) also favouring phenobarbital (5.5 vs 15 minutes, p < 0.1). Two of 18 on phenobarbital convulsed for more than 10 minutes compared with eight of 18 on diazepam/phenytoin (relative risk for diazepam/phenytoin = 4 [95% CI 1.03 to 16.3]).

A retrospective review of very high dose phenobarbital for refractory status epilepticus in children published in 1988, presented 50 children aged from newborn to 13 years. All were treated with very high dose phenobarbital, without reference to any predetermined maximum levels or doses. The authors found no maximum dose beyond which further doses were likely to be ineffective. More recently three children with refractory status epilepticus were described, in whom seizures were not controlled with usual doses of intravenous phenobarbital or phenytoin. The authors found that very high doses phenobarbital of up to 80mg/Kg per day were effective in achieving seizure control.

A few animal studies have been performed. The effects were compared of three different anti-epileptic drugs on adult rats with status epilepticus caused by continuous electrical hippocampal stimulation. Two thirds (26 of 38) rats treated with phenobarbital had electrographic suppression of status epilepticus within the first two hours of drug administration, compared with none of 16 control rats and one of 37 treated with phenytoin. Phenobarbital appeared to have greater efficacy when given one hour after induction of status epilepticus, than when given at four hours. Additionally when those that survived were monitored eight weeks later, 12 of 31 Phenobarbital treated rats had evidence of epilepsy, compared with eight of ten control rats and 24 of 30 phenytoin treated rats. Mortality rates were not significantly affected by the treatment.
Another, smaller, study in rats used electric current to induce status epilepticus. Ten minutes later, infusion of either phenobarbital or phenytoin was started. In those given phenobarbital, although convulsive activity was suppressed in a mean of 30 minutes, higher phenobarbital doses were required to suppress all electrical epileptiform activity. All six rats survived without ventilatory support until sacrifice a few hours later. The six rats given phenytoin took longer to stop convulsive activity, and it was not possible to achieve suppression of electrical activity without the animal dying. All six rats died within 45 minutes of spiking ceasing (four within five minutes).

10c. Summary of available estimates of comparative effectiveness

The Cochrane review found that it was not possible to combine information from the Treiman and Shaner paper to provide an estimate of comparative effectiveness of diazepam plus phenytoin versus phenobarbital as the test for heterogeneity was significant, and the type of status epilepticus studied was different. Hence only the data already provided in 10b are available.

11. Summary of comparative evidence on safety:

11a. Estimate of total patient exposure to date

Oral Phenobarbital has been available as an antiepileptic drug since 1912. There are no data available on patient exposure to oral phenobarbital, but it is likely that more than 20 million person/years of exposure has been accumulated. Parenteral phenobarbital has been used since the 1920s. There are no data available on patient exposure to parenteral phenobarbital, but it has probably been used in more than 500,000 people worldwide.

11b. Description of adverse effects/reactions

The most frequent adverse event of phenobarbital administration is sedation. Overdosage can be fatal – toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock; hypothermia may occur. Necrosis has followed extravasation, and intravenous injection can cause hypotension, shock, laryngospasm and apnoea. Hypersensitivity reactions occur occasionally. Skin reactions can occur, but exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis are very rare. Hepatitis and disturbances of liver function have been reported.
11c. Identification of variation in safety due to health systems and patient factors

Many side-effects of phenobarbital, such as respiratory and cardiovascular depression are serious and could require treatment which may not be available in resource-poor countries. It is clear, however, from section 11d (see below) that the complications occur no more frequently with phenobarbital than with the other anticonvulsants, and some could be complications of the status epilepticus rather than the treatment.

11d. Summary of comparative safety against comparators

The study comparing only intravenous phenobarbital and the diazepam/phenytoin combination found that the frequency of complications, including arrhythmias and hypotension, was similar in the two groups, although the study lacked the power to detect uncommon complications 19. One third of patients in each group were intubated, but this was for a variety of reasons, occasionally occurring before initiation of therapy. The study was also unable to distinguish between sedation due to medication from that due to status epilepticus.

The larger study of four treatments for generalised status epilepticus found no significant difference among the treatments in the number of specified side-effects experienced 24. There was also no difference among the groups in those experiencing each of the specified side-effects; hypoventilation (9.9 to 16.8%, chi squared = 2.73, df = 3, p = 0.44); hypotension (25.8 to 34.1%, Chi squared = 2.13, df = 3, p = 0.55); cardiac-rhythm disturbance (2.1 to 7.2%, Chi squared not valid, phenobarbital versus the rest, Fisher’s exact 2-sided p = 0.60). Of those given phenobarbital 13% experienced hypoventilation, 34% hypotension and three percent cardiac rhythm disturbance.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

The International Drug Price Indicator Guide is currently unavailable. MSF lists phenobarbital sodium 200mg/ml, 1 ml amp at 0.11Euro per unit (available from MSF-Supply), and 100mg/ml, 2ml amp also at 0.11 Euro per unit (available only from MSF-Holland). The WHO Regional Office for Africa Essential Medicines price indicator (2003) lists parenteral phenobarbital (100mg/ml ampoule) at 8.3 US dollars per 100 ampoules (ex works price, available from the International Dispensary Association) 1. The UK price is £1.80 per 1ml ampoule of 200mg.

No formal comparative cost-effectiveness studies have been performed.
13. **Summary of regulatory status of the medicine**

   In the UK, phenobarbital licence is for treatment of all forms of epilepsy except absence seizures; parenteral phenobarbital is licensed for status epilepticus. This licence is currently held by Cardinal Health Martindale.

14. **Availability of pharmacopoeial standards**

   Parenteral phenobarbital is listed in most drugs catalogues. These include the British, International, European, Brazilian, Chinese, Polish, USA and Vietnamese Pharmacopoeias.

15. **Proposed text for the WHO Model Formulary**

   The following is adapted from the MSF22.

**PHENOBARBITAL**

**Therapeutic action**
- Anticonvulsant, sedative

**Indications**
- Status epilepticus: prolonged seizures or repeated seizures at short intervals without consciousness recovery

**Presentation and route of administration**
- 200mg in 1 ml ampoule (200 mg/ml) for deep IM or slow and diluted IV injection. Also available as 100mg/ml ampoules.

**Dosage**
- Child: 15 to 20 mg/kg by slow IV injection
- Adult: 10 mg/kg by slow IV injection (at a rate of 50-75 mg/minute maximum)
- Phenobarbital solution must be diluted: 1 ml in 10 ml water for injection

**Duration**: according to clinical response

**Contra-indications, adverse effects, precautions**
- Do not administer in severe respiratory depression
- Assisted ventilation is essential in case of respiratory distress
- May cause: drowsiness, respiratory depression
- Risk of increased sedation when combined with alcohol and drugs acting on the central nervous system such as diazepam, chlorphenamine, chlorpromazine
- *Pregnancy and breast-feeding: risks linked to status epilepticus appear greater than risks linked to Phenobarbital*
Remarks

- For febrile convulsions in children, use diazepam by parental or rectal route
- In the treatment of status epilepticus, administer first diazepam (rapid effect) rectally or by slow IV route, then Phenobarbital (prolonged effect) by slow IV route
- Phenobarbital should be injected in glass syringe; if not available, inject immediately after filling the plastic syringe
- SC route may cause necrosis
- Do not mix with other drugs in the same syringe
- Warning: comes in ampoules of different strengths. Before any injection, check concentration
- Phenobarbital is subject to international controls: follow national regulations
- Injectable Phenobarbital is not included in the WHO list of essential drugs
- Storage: no special temperature requirements – very sensitive to light

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Reference List


