Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Satal Forte – Phenobarbital Sodium 200mg in 1ml Solution for Injection

2. Qualitative and quantitative composition
Each 1ml of Phenobarbital sodium 200mg in 1 ml solution for injection contains 200mg of Phenobarbital Sodium.
Excipients of know effects: Propylene Glycol
For the full list of excipients, see section 6.1

3. Pharmaceutical form
Solution for Injection.

4. Clinical particulars
4.1 Therapeutic indications
An anti-convulsant for the treatment all forms of epilepsy except absence seizures.

4.2 Posology and method of administration
Posology
Adults
50 - 200mg as a single dose by intramuscular, subcutaneous or, after dilution 1 in 10 with Water for Injection, by intravenous injection, repeated, if necessary, after 6 hours.

Paediatric population
3 - 5mg per kg body weight as a single dose by intramuscular injection.

Method of administration
Intramuscular, subcutaneous or intravenous injection

4.3 Contraindications
Hypersensitivity to phenobarbital, other barbiturates or to any of the excipients listed in section 6.1 Severe respiratory depression.
Acute intermittent porphyria.
Severe impairment of renal or hepatic function.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour.
The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Phenobarbital Sodium.
Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Steven-Johnson syndrome and toxic epidermal necrolysis
Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenobarbital. Patients should be advised of the signs and symptoms and

monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
If symptoms or signs of SJS or TEN (e.g., progressive skin rash often with blisters or mucosal lesions) are present, Phenobarbital treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of phenobarbital, phenobarbital must not be re-started in this patient at any time.

Phenobarbital should be used with caution in the young, elderly, senile or debilitated patient and those with renal impairment, existing liver disease or respiratory depression, (should be avoided if severe), pregnancy, breastfeeding and porphyria.
Prolonged use may result in dependence of the alcohol-barbiturate type and care must be taken in treating patients with a history of drug abuse or alcoholism.

Intravenous use must be preceded by dilution as described in section 4.2. Subcutaneous injection can cause tissue necrosis.

Sudden withdrawal should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, fits and delirium) may be precipitated.

Acute chronic pain – paradoxical excitement may be induced or important symptoms masked.

Herbal preparations containing St John's wort (Hypericum perforatum) should not be used while taking phenobarbital due to the risk of decreased plasma concentrations and reduced clinical effects of phenobarbital

Excipient warning

Propylene glycol in high doses may cause central nervous system side-effects, lactic acidosis, kidney and liver toxicity, increase in plasma osmolarity, and hemolytic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effects on Phenobarbital

- Alcohol – concurrent administration with alcohol may lead to an additive CNS depressant effect. This is likely with concurrent administration with other CNS depressants.
- Antidepressants – including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold
- Antiepileptics - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin and sodium valproate. Vigabatrin possibly decreases phenobarbital plasma concentrations.

- Antipsychotics – concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug.
- Folic acid – if folic acid supplements are given to treat folate deficiency, which can be caused by the use of phenobarbital, the serum phenobarbital levels may fall, leading to decreased seizure control in some patients. (see section 4.6).
- Memantine – the effect of Phenobarbital is possibly reduced.
- Methylphenidate – plasma concentration of Phenobarbital is possibly increased.
- St John's wort (Hypericum perforatum) – the effect of phenobarbital can be reduced by concomitant use of the herbal remedy St John's wort.

Effects of phenobarbital on other medicines

Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs:

- Anti-arrhythmics – disopyramide and quinidine loss of arrhythmia control is possible. Plasma levels of anti-arrhythmics should be monitored, if phenobarbital is added or withdrawn. Changes in dosage may be necessary.
- Antibacterials – chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital.
- Anticoagulants.
- Antidepressants – paroxetine, mianserin and tricyclic antidepressants.
- Antiepileptics – carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly ethosuxamide.
- Antifungals – the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations of itraconazole or posaconazole. Avoid concomitant use of voriconazole.
- Antipsychotics – phenobarbital possibly reduces concentration of aripiprazole.
- Antivirals – phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir.
- Anxiolytics and Hypnotics – clonazepam.
- Aprepitant – phenobarbital possibly reduces plasma concentration of aprepitant.
- Beta-blockers – metoprolol, timolol and possibly propranolol.
- Calcium channel blockers – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required.
- Cardiac Glycosides – blood levels of digitoxin can be halved by concurrent use.
- Ciclosporin or tacrolimus.
- Corticosteroids.
- Cytotoxics – phenobarbital possibly reduces the plasma levels of etoposide or irinotecan.
- Diuretics – concomitant use with eplerenone should be avoided.
- Haloperidol- serum levels are approximately halved by concurrent used with phenobarbital.

- Hormone Antagonists – gestrinone and possibly toremifene.
- Methadone – levels can be reduced by concurrent use of phenobarbital and withdrawal symptoms have been reported in patients maintained on methadone when phenobarbital has been added. Increases in the methadone dosage may be necessary.
- Montelukast.
- Oestrogens – reduced contraceptive effect.
- Progestogens – reduced contraceptive effect.
- Sodium oxybate – enhanced effects, avoid concomitant use.
- Theophylline – may require an increase in theophylline dose.
- Thyroid hormones - Phenobarbital has been shown to accelerate the metabolism of levothyroxine and liothyronine. Prescribers should be alert for changes in thyroid status if barbiturates are added or withdrawn from patients being treated for hypothyroidism.
- Tibolone
- Tropisetron
- Vitamins – barbiturates possibly increase requirements for vitamin D

Phenobarbital may interfere with some laboratory tests including metyrapone test, phentolamine tests and serum bilirubin estimation.

4.6 Pregnancy and Lactation

Phenobarbital therapy in epileptic pregnant women presents a risk to the foetus in terms of major and minor congenital defects such as congenital craniofacial, digital abnormalities and, less commonly, cleft lip and palate. The risk of teratogenic effects developing appears to be greater if more than one antiepileptic drug is administered. The risk to the mother however is greater if phenobarbital is withheld and seizure control is lost. The risk: benefit balance, in this case, favours continued use of the drug during pregnancy at the lowest possible level to control seizures.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy (see section 4.5). Folic supplementation during pregnancy can help to counteract the risk of neural tube defects.

Phenobarbital readily crosses the placenta following oral administration and is distributed throughout foetal tissue, the highest concentrations being found in the placenta, foetal liver and brain. Adverse effects on neurobehavioral development have also been reported.

Haemorrhage at birth is also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as the neonate) is recommended, the neonate should be monitored for signs of bleeding.

Breast-feeding

Phenobarbital is excreted into breast milk and may cause sedation in the infant though the risk is probably small. Breastfeeding is therefore not recommended.

4.7 Effects on ability to drive and use machines

Phenobarbital may impair the mental and/or physical abilities of the patient. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Antiepileptic hypersensitivity syndrome may occur. Symptoms include fever, rash, lymphadenopathy and hepatitis.

Tabulated summary of adverse reactions

Adverse events are listed below by system organ class and frequency.

Term	**Frequency of occurrence**
Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1 000 to <1/100)
Rare	(≥1/10 000 to <1/1 000)
Very rare	(<1/10 000)
Not known	(cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Not known	Megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia
Metabolism and nutritional disorders	Not Known	Osteomalacia, rickets
Psychiatric disorders	Not Known	Paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy
Nervous system disorders	Not known	Hyperactivity, behavioural disturbances in children, ataxia, nystagmus
Cardiac disorders	Not known	Hypotension
Respiratory disorders	Not known	Respiratory depression
Hepato-biliary	Not known	Hepatitis, cholestasis

Skin and subcutaneous tissue disorders	Not Known	Allergic skin reactions (maculopapular morbilliform or scarlatiniform rashes), other skin reactions such as exfoliative dermatitis, erythema multiforme. Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4) very rarely
Musculoskeletal, connective tissue and bone disorders	Not Known	There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with Phenobarbital. The mechanism by which Phenobarbital affects bone metabolism has not been identified.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

Symptoms

These include drowsiness, dysarthria, ataxia, nystagmus and disinhibition. There may also be coma, hypotension, hypotonia, hyporeflexia, hypothermia, and respiratory and cardiovascular depression. The duration and depth of cerebral depression varies with the dose and the tolerance of the patient.

Management

Supportive measures alone may be sufficient if symptoms are mild. If an overdose of solution for injection is given, or erroneously taken by mouth, the prime objective of treatment is to maintain vital functions, respiration, cardiovascular and renal functions and the electrolyte balance while the majority of the drug is metabolised by hepatic enzymes. Given normal renal function, forced alkaline diuresis (maintaining the urinary pH at approximately 8 by intravenous infusion) may enhance the excretion of the drug from the kidneys.

Charcoal hemoperfusion is the treatment of choice for the majority of patients with severe barbiturate poisoning who fail to improve or who deteriorate despite good supportive care.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, barbiturates and derivatives ATC Code: N03A A02.

Phenobarbital is a long-acting barbiturate, which because of its depressant effect on the motor cortex, is used

in the treatment of epilepsy. Phenobarbital has a widespread depressant action on cerebral function.

It has selective anticonvulsant activity and, used in hypnotic doses, it alters the stages of sleep in a dose dependent manner.

It has sedative effects and has some protective action against all varieties of human partial and generalised epilepsy, with the exception of absence seizures. Phenobarbital is also effective in preventing seizures in the corresponding experimental animal models of epilepsy.

In different studies phenobarbital appears to have had inconsistent effects in suppressing experimental epileptic foci, and epileptic after-discharges, but it inhibits synaptic transmission, at least in the spinal cord. The drug's probable biochemical mechanism of action is through prolonging the opening time of Cl- ion channels in postsynaptic neuronal membranes. This effect causes membrane hyperpolarisation and thus impairs nerve impulse propagation. Phenobarbital also decreases intraneuronal Na+ concentrations, and inhibits Ca2+ influx into depolarised synaptosomes. It raises brain serotonin levels, and inhibits noradrenaline (norepinephrine) reuptake into synaptosomes. These additional biochemical actions may contribute towards the anticonvulsant effects of the drug.

5.2 Pharmacokinetic properties

Metabolism

The plasma half-life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. The half-life is increased in the elderly and in neonates and is prolonged by renal and hepatic disorders. There is a considerable interindividual variation in Phenobarbital kinetics. Phenobarbital is only partly metabolised in the liver.
It is about 40% plasma bound.

Elimination

Excretion is mainly in the urine (and is increased in alkaline urine) with about 30% of the drug unchanged. The remainder is inactivated in the liver.
Phenobarbital crosses the placenta and is secreted in the milk of nursing mothers.

5.3 Preclinical safety data

No additional pre-clinical data of relevance to the prescriber is available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Disodium Edetate, Propylene Glycol, Ethanol, Sodium hydroxide, Hydrochloric acid and Water for Injection.

6.2 Incompatibilities

None

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage
Do not store above 30°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and Content of container
Clear glass ampoules, glass type I, Ph. Eur. Pack sizes: 5 x 1ml and 10 x 1 ml

6.6 Special precautions for disposal and other handling
None

7. Marketing Authorization Holder
Tasa Pharma Limited Unit C1-C3
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8. Marketing Authorization Number
H2022/CTD10125/22976

9. Date of first authorization/renewal of the authorization
2023 September 04

10. Date of revision of the text
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