Enodama 125mg Tablets

Summary of Product Characteristics Updated 11-May-2023 | Desitin Pharma Ltd

1. Name of the medicinal product

Enodama 125mg Tablets

2. Qualitative and quantitative composition

Each tablet contains 125mg primidone.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets

White to off-white, circular, biconvex, uncoated tablet debossed with 'TL' on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

'Primidone' is indicated in the management of grand mal and psychomotor (temporal lobe) epilepsy. It is also of value in the management of focal or Jacksonian seizures, myoclonic jerks and akinetic attacks.

Management of essential tremor.

4.2 Posology and method of administration

Posology

Primidone should be started at the lowest possible dose in the evening and thereafter the dose should be increase in a stepwise manner to minimise adverse reactions.

Epilepsy

Treatment must always be planned on an individual basis. In many patients primidone treatment may be given as monotherapy, but in some, Primidone will need to be combined with other anticonvulsants or with supporting therapy.

In certain patients, it may be advisable to give a larger dose when the seizures are more frequent. For instance:

1) If the attacks are nocturnal then all or most of the daily dose may be given in the evening;

2) If the attacks are associated with some particular event such as menstruation, a slight increase in the appropriate dose is often beneficial.

In adults:

Initial dose: it is usually 125mg in a single intake in the evening. Then every 3 days, the daily dose is increased in a stepwise approach by 125mg until the patient is receiving 500mg daily. Thereafter, every 3 days, the daily dose (given in 2 divided doses) is increased by 250mg, until control is obtained or until the maximum tolerated dose and may be up to 1.5g daily.

Maintenance dose:

	Milligrams
Adults	750 - 1500

In children:

Initial dose: it is usually 125mg in a single intake in the evening. Then every 3 days, the daily dose is increased in a stepwise approach by 125mg until the patient is receiving 500mg daily. Thereafter, every 3 days, the daily dose (given in 2 divided doses) is increased by 250mg in children over the age of 9 and by 125mg in children under 9 years until control is obtained or until the maximum tolerated dose in children.

Maintenance doses:

	Milligrams
Children over 9 years	750 to 1500
Children 6 to 9 years	750 to 1000
Children 2 to 5 years	500 to 750

Children up to 2 years	250 to 500

Concomitant use/switch from other anticonvulsant treatments

In case of lack of efficacy of other anticonvulsant treatments or in case of adverse reactions induced by these drugs, primidone may be used to increase the efficacy of the existing/underlying treatment or to replace it. At first, primidone should be added to the previous treatment following a method of progressive dose increase as previously described. When an appreciable/acceptable therapeutic effect is reached and primidone dose has reached at least half of the previous dose, the discontinuation of the previous treatment can be attempted. This dose adjustment is to be performed progressively for a period of 2 weeks during which it could be necessary to increase primidone doses to maintain a good control.

Withdrawal of previous treatment should not be too rapid or status epilepticus may occur. Where phenobarbital formed the major part of the previous treatment, however, both its withdrawal and Primidone substitution should be made earlier, so as to prevent excessive drowsiness from interfering with accurate assessment of the optimum dosage of Primidone.

Essential tremor

Initially a dose of 50mg daily should be introduced in a single intake late afternoon, using, when available, the 50mg tablet. The daily dose (given in 2 divided doses) should be increased gradually over a 2 to 3-week period until remission of symptoms or the highest dose tolerated up to a maximum of 750mg daily.

Patients not previously treated with anticonvulsants

Patients with essential tremor who have not previously been exposed to anticonvulsants, or other drugs known to induce increased hepatic enzyme activity, may experience acute symptoms of intolerance to Primidone, frequently characterised by vertigo, unsteadiness and nausea. It is, therefore, essential to respect initial dose therapeutic regimen.

Special population

Patients with renal impairment

Due to decrease renal elimination of primidone in patients with renal insufficiency, the dose should be adjusted according to clinical response and biological monitoring.

Patients with hepatic impairment

Due to the possible altered conversion of primidone to its metabolites and reduced elimination of phenobarbital in patients with severe hepatic impairment, the dose should be adjusted according to clinical response and biological monitoring.

Elderly patients

It is advisable to monitor elderly patients with reduced renal function who are receiving primidone.

Method of administration

Oral use

The tablets should be swallowed whole with a glass of water.

4.3 Contraindications

• Hypersensitivity to the active substance primidone, to phenobarbital or to any of the excipients listed in section 6.1

• Acute intermittent porphyria

• Concomitant use with certain classes of medicinal products (see section 4.5)

4.4 Special warnings and precautions for use

Special warnings

Primidone is not efficient for the treatment of absences and myoclonic fits which may be sometimes aggravated.

Due to its sedative effect it is recommended to initiate treatment of primidone with the lowest dose in the evening, and then with a stepwise approach (see section 4.2).

Primidone should be given with caution and may be required in reduced dosage in children, the elderly, debilitated patients or those with impaired renal, hepatic or respiratory function.

Primidone has the potential to harm the foetus (see section 4.6).

Crisis aggravation

Introduction of an anti-epileptic drug may be rarely followed by recrudescence of the crises or by occurrence of new type of crisis for the patient, independently of the fluctuations observed in some epilepsy. For primidone, causes of these aggravations may be: a choice of a treatment inadequate for the crises or the epileptic syndrome in this patient, a

change of the concomitant anti-epileptic treatment or a pharmacokinetic interaction, a toxicity or overdose. There could be no other explanation than a paradoxal reaction.

Treatment cessation

Sudden withdrawal of a treatment at efficient anti-epileptic doses may induce convulsive fits and epilepticus status, mainly in case of alcoholism added.

Primidone is a potent CNS depressant and is partially metabolised into phenobarbital. After prolonged administration there is a potential for tolerance, dependence and a withdrawal reaction on abrupt cessation of treatment.

Prevention of vitamin deficiencies

Primidone is an enzymatic inducer (CYP450) which may increase the catabolism of vitamin D. A dose-dependent increase in the risk of osteomalacia has been observed during therapy with primidone, which may predispose to the development of bone disease. Vitamin D supplementation may be needed during long-term primidone therapy (see section 4.8).

Exceptionally, as with phenytoin and phenobarbital, megaloblastic anaemia may develop requiring discontinuation of primidone. This condition may respond to treatment with folic acid and/or vitamin B_{12} (see section 4.8).

Suicidal behaviour

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 primidone.

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.

Severe skin reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of primidone.

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, primidone 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 primidone (or phenobarbital), primidone must not be re-started in this patient at any time. (see section 4.8)

Precautions for use

Primidone, as phenobarbital, is an enzymatic inducer and is thus susceptible to reduce efficacy of some medicinal products via progressive increase of their metabolism (see section 4.5).

Concomitant intake of this medicinal product with alcoholic beverages or with medicinal products containing alcohol is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Primidone and its main metabolite phenobarbital are strong inducers of cytochrome P450 and thus lead to life-threatening situations due to the risk of decreased plasma concentrations and risk of lack of efficacy of co-administered medications.

• Risk of decreased plasma concentrations due to increased metabolism induced by primidone for:

- Antivirals: cobicistat, daclatasvir, dasabuvir, ledipasvir, nelfinavir, rilpivirine, ombitasvir+paritaprevir, sofosbuvir, telaprevir.

- Antifungal agents: voriconazole, isavuconazole.

- Drugs affecting nervous system* (except anti-epileptics): lurasidone.

- Anti-infectious agents: delamanide.

• Risk of decreased primidone plasma concentrations and risk of lack of efficacy for:

- St John's wort.

Concomitant use not recommended

• Risk of decreased plasma concentrations due to increased metabolism induced by primidone for:

- Drugs affecting nervous system* (except anti-epileptics): mianserin, oxycodone, quetiapine, sertraline.

- Anti-infectious agents: telithromycine, bedaquiline.

- Anti-neoplastic agents: tyrosine kinase inhibitors, ifosfamide (+ risk of increased neurotoxicity of ifosfamide due to increased metabolism induced by primidone).

- Antivirals: boceprevir, simeprevir.

- Antifungal agents: itraconazole.

- Anticoagulant drugs: apixaban, dabigatran, rivaroxaban, ticagrelor.

- Cardiovascular agents: bosentan, nimodipine, dronedarone, macitentan, ranolazine).

- Hormonal agents: abiraterone, ulipristal.

- Other therapeutic classes: alcohol (+ increased risk of sedative effects of primidone and alcohol), estro-progestative contraceptive (use preferably another contraceptive method during combination and the following cycle), ivacaftor, praziquantel.

Precautions including dose adjustment:

• Risk of decreased plasma concentrations due to increased metabolism induced by primidone for:

- Other anti-epileptics: carbamazepine; felbamate; lamotrigine; oxcarbazepine (+ risk of decreased plasma levels of primidone by increased metabolism induced by oxcarbazepine); perampanel; phenytoin (+ risk of increased phenobarbital concentrations and possible toxicity. Possible toxicity with phenytoin on stopping primidone); stiripentol, tiagabine, valproic acid, zonisamide.

- Drugs affecting nervous system* (except anti-epileptics): benzodiazepines, methadone, opioid agents (including fentanyl).

- Anti-infective agents: doxycycline, metronidazole, quinine (+ risk of increased phenobarbital concentrations and possible toxicity).

- Anti-neoplastic agents: carbazitaxel, docetaxel, irinotecan, procarbazine (+ risk of increased hypersensitivity reactions: hypereosinophilia, rash).

- Antivirals: dolutegravir; maraviroc; protease inhibitors in combination with ritonavir (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir): risk of decreased primidone concentrations due to CYP3A4 significant inhibition properties of the combination protease inhibitors-ritonavir.

- Antifungal agents: albendazole, posaconazole.

- Anticoagulant drugs: antivitamin K drugs (acenocoumarol, phenindione, warfarin): INR monitoring required.

- Cardiovascular agents: calcium channel blockers; beta-blockers (metoprolol, propranolol); class I A antiarrhythmic, ivabradine, propafenone.

- Hormonal agents: androgens; glucocorticosteroids and mineralocorticosteroids; thyroid hormones.

- Other therapeutic classes: non-contraceptive estrogens; folates; immunosuppressant agents (cyclosporin, tacrolimus, sirolimus, everolimus); iron-chelators (deferasirox); theophylline.

* The drugs affecting the nervous system also have increased risk of additive CNS depression.

4.6 Fertility, pregnancy and lactation

Pregnancy

Primidone is suspected to have caused serious birth defects when administered during pregnancy. Available data confirmed the increased incidence of congenital defects, particularly palatine and/or labial clefts, cardiovascular malformations and hypospadias. Face dysmorphia, microcephaly, nail hypoplasia have been also reported. Published data suggest a dose-effect relationship but it has to be confirmed. Contraception is therefore advised however women should be advised that primidone may cause the contraceptive pill to be ineffective.

Studies in animals have shown reproductive toxicity, including teratogenicity and effects on memory and learning (see section 5.3).

Women planning a pregnancy and pregnant women:

A pre-conception visit is recommended where the patient should be informed about the risks of treatment and treatment cessation during pregnancy.

If the treatment with primidone is to be maintained during pregnancy:

• The minimal effective dose should be used;

• Given its beneficial effect in other situations, supplementation with folic acid can be suggested before and during pregnancy. The effectiveness of this supplementation is not confirmed.

Neonate

Withdrawal symptoms may occur in the newly born whose mothers have received primidone during late pregnancy.

Anticonvulsant therapy in pregnancy has occasionally been associated with coagulation disorders in the neonates. For this reason, pregnant patients should be given Vitamin K1 through the last month of pregnancy up to the time of delivery. In the absence of such pretreatment, 10mg Vitamin K1 may be given to the mother at the time of delivery and 1mg should be given immediately to the neonate at risk.

Breast-feeding

Due to the risk of sedation which may induce difficulties in suckling responsible of poor weight gain during the neonatal immediate period, breast-feeding is not recommended.

Fertility

No human data on the effect of primidone on fertility are available.

In animals, effects on fertility have been observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Due to the risk of somnolence, visual disturbances and impaired reaction time, primidone has a major impact on the ability to drive and use machines.

4.8 Undesirable effects

At treatment initiation, the most common side effects are drowsiness, dizziness and ataxia; they may disappear with treatment continuation and/or posology reduction.

On occasions an idiosyncratic reaction may occur which involves visual disturbances, nausea, headache, dizziness, vomiting, nystagmus and ataxia; these symptoms are usually transient even when pronounced. In an acute and severe form, withdrawal of treatment is required.

Other adverse reactions, observed during post-marketing setting, may include:

Frequencies are defined as: very rare (< 1/10,000), not known (cannot be estimated from the available data).

Frequency	System Organ Class	Adverse reactions
Common (>1/100, <1/10)	Eye disorders	Visual disturbances
	Nervous system disorders	Apathy, ataxia, nystagmus
	Gastrointestinal disorders	Nausea
Uncommon (>1/1,000, <1/100)	Nervous system disorders	Headache, dizziness
	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders	Allergic reactions particularly affecting the skin which can include maculopapular, morbilliform or scarlatiniform rashes
Rare (>1/10,000, <1/1,000)	Blood and lymphatic system disorders	Megaloblastic anemia*, leucopenia, thrombocytopenia, lymphadenopathy
	Psychiatric disorders	psychotic reactions
	Musculoskeletal and connective tissue disorders	Arthralgia, osteomalacia** As with phenobarbital, Dupuytren's contracture
	Skin and subcutaneous tissue disorders	Exfoliative dermatitis, lupus erythematosus.
	Investigations	Elevation in hepatic enzymes, including gamma-glutamyl transferase (gamma GT) and alkaline phosphatase
Very rare (<1/10,000)	Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions : Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4)

Unknown	Immune system disorders	Hypersensitivity syndrome: multisystemic reactions often with fever, rash, hypereosinophilia and liver injury
	Musculoskeletal and connective tissue disorders	Decreased bone density, osteopenia, osteoporosis and fractures in patients on long term therapy***

* Exceptionally, as with phenytoin and phenobarbital, primidone can cause megaloblastic anaemia requiring discontinuation of primidone. This condition may respond to treatment with folic acid and/or Vitamin B12.

** Vitamin D supplementation may be needed during long-term Primidone therapy, since vitamin D catabolism may be increased.

*** The mechanism by which affect bone metabolism has not been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website : www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Primidone is metabolised extensively to phenobarbitone and overdosage leads to varying degrees of CNS depression which, depending on the dose ingested, may include ataxia, loss of consciousness, respiratory depression and coma.

Crystalluria may occur in overdosage and could be used as a helpful diagnostic aid where primidone overdosage is suspected.

Depending on the severity of intoxication, therapy should include aspiration of stomach contents, administration of activated charcoal, administration of intravenous fluids, forced alkaline diuresis (striving for a urine pH of 8.0), and general supportive measures. In more life threatening circumstances, haemoperfusion (if the patient is hypotensive) or haemodialysis are effective.

There is no specific antidote.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics (barbiturates and derivatives), ATC code: N03AA03

Primidone is an anticonvulsant largely metabolised into two main metabolites phenobarbital and phenylethylmalonamide (PEMA). The relative contribution of these three moieties to the clinical anticonvulsant effect has not been firmly established.

In addition, primidone has been demonstrated to suppress tremor, with a possible contribution of these metabolites.

Although the precise mode of action of Primidone is unknown, in common with other anticonvulsants, effects on the neuronal membrane particularly with respect to alteration of ionic fluxes are likely to play a fundamental role.

Primidone, as with other anticonvulsants, can induce liver enzymes.

5.2 Pharmacokinetic properties

Absorption

Primidone is absorbed rapidly from the gastrointestinal tract, peak plasma levels being attained approximately 3 hours after ingestion, therapeutic blood concentration known to be between 5 to 10 mg/ml.

Distribution

Primidone is well distributed in all organs and tissues: it crosses the blood-brain and placental barriers and is excreted in breast milk (see section 4.6). Primidone is only partially bound to plasma proteins (by about 35%) whereas approximately half of phenobarbital is bound.

Metabolism

Primidone is partially metabolised in the liver into phenobarbital and phenylethylmalonamide (PEMA), its major metabolites, that both have anticonvulsant activity and complex pharmacokinetic properties.

Primidone, as other anticonvulsants, can induce liver enzymes (see sections 4.4 and 4.5)

Elimination

Primidone has an elimination half-life of approximately 10 hours which is considerably shorter than those of its principal metabolites: PEMA (10 to 25 hours) and phenobarbital (50 to 160 h). Elimination is mainly the urinary with 40% as unchanged drug and 28% as PEMA.

5.3 Preclinical safety data

Repeated dose toxicity

Centrilobular hepatocyte hypertrophy and chronic nephropathy have been observed in rats administered clinically relevant doses of primidone for 14-weeks. Hepatocellular hypertrophy has also been observed in dogs administered clinically relevant doses of primidone for 6-months.

Genotoxicity

Primidone was shown to be mutagenic in one strain of Salmonella typhimurium strain (TA1535). Other in vitro and in vivo tests did not demonstrate genotoxicity. Therefore, the risk of genotoxicity to humans is unknown.

Carcinogenicity

Standard 2-year carcinogenicity studies have identified an increased incidence of hepatocellular neoplasms in male and female mice, thyroid adenomas in male mice and male rats, and combined incidences of renal tubule adenomas or carcinomas in male rats at doses considered clinically relevant. The risk of carcinogenicity to humans is unknown.

Reproductive toxicity

Animal studies have shown that primidone is teratogenic and impairs post-natal development at doses considered to be clinically relevant. Teratogenic effects in mice included palatal defects, enlargement of cerebral ventricles, club foot, open eyes and haemorrhages within the subarachnoid space. Primidone was also shown to be embryolethal in mice and rats at clinically relevant doses. Post-natal development effects include impairment of memory and learning development in male rats from litters of dosed female rats. Effects on fertility in animals have been observed at doses considered to be clinically relevant. Primidone induced a reduction in seminal vesicle weight and an increase in estrous cycle length in mice. In a 5-day study in male mice, primidone induced a dose-dependent increase in sperm-head abnormalities.

6. Pharmaceutical particulars

6.1 List of excipients

Carmellose calcium

Magnesium stearate

Povidone

Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottle containing 100 tablets, fitted with a child resistant white plastic cap consists of polypropylene inner, polypropylene outer with white colorant and liner.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Desitin Arzneimittel GmbH

Weg beim Jäger 214

22335 Hamburg

Germany

8. Marketing authorisation number(s)

PL 14040/0038

9. Date of first authorisation/renewal of the authorisation

Date of First Authorisation: 28th Feb 2022

10. Date of revision of the text

19/12/2022

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