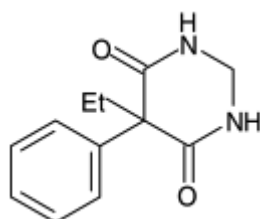


Product Information

January 2009/Version 2.3

Mysoline® (Primidone) Tablets BP

Link Pharmaceuticals Australia Pty Ltd



COMPOSITION:

Active: Primidone

Inactive: Povidone, carmellose calcium, gelatin (E441), magnesium stearate (E572), stearic acid (E570)

DESCRIPTION:

Chemical Name: 5-ethyl-5-phenyl-2,3-dihydropyrimidine-4,6(1H,5H)-dione

Molecular Formula: C₁₂H₁₄N₂O₂. **MW:** 218.3. **CAS No:** [125-33-7]

It is a highly stable, crystalline substance with a slightly bitter taste. It is only sparingly soluble in water (approximately 60 mg/100 mL at 37 deg. C) and in most organic solvents. Unlike phenobarbitone it does not possess any acidic properties.

PHARMACOLOGY:

Animal studies have indicated that the anticonvulsant properties of Mysoline are attributable partly to primidone itself and partly to its metabolites phenobarbitone and phenylethylmalonamide. The drug reduces the sensitivity of the central nervous system to fit inducing stimuli but its precise mode of action is obscure, although enhancement of release of inhibitory transmitters may possibly occur.

Like phenobarbitone and phenytoin, Mysoline modifies the maximal (tonic-clonic) seizure pattern induced in rats by electrical stimulation, and at 5 mg/kg it is twice as potent as phenobarbitone in abolishing the tonic extensor component of the seizure.

Mysoline also has the ability to raise the threshold for minimal electroshock seizures in both normal and hyponatraemic animals, and to prevent experimental psychomotor seizures in mice and rats. Mysoline has been shown to be an effective antagonist to leptazol-induced convulsions. Unlike phenytoin, it will prevent the tonic component of maximal convulsions as well as raise the seizure threshold.

Pharmacokinetics:

The rate of absorption of primidone in humans is relatively rapid, though somewhat variable between individuals. In epileptic patients a single 500 mg dose gave a peak plasma concentration of 2.7 +/- 0.4 microgram/mL, even though the time to peak varied markedly. The elimination half-life in epileptic patients is 8 +/- 1 hours, and similar values have been obtained in healthy volunteers and in epileptic children. In uraemic subjects, the half-life increased to 13.9 hours, but this reduced to 5.1 hours during dialysis. Steady-state drug levels in chronic seizure patients (3.2 to 12.7 microgram/mL) were directly proportional to the daily dose (250 to 1,250 mg).

Metabolism involves conversion to two major metabolites, phenylethylmalonamide (PEMA) and phenobarbitone (PB), both of which have some degree of anticonvulsant activity. Metabolism to PB is slow and not linearly related to dose. Conversion to PEMA is proportional to dose and this compound is cleared with an apparent half-life of 22 to 24 hours. The hydroxylated parent drug has also been identified as a minor metabolite.

Primidone and its metabolites readily cross the blood-brain barrier with ratios in cerebrospinal fluid/plasma of 1.1, 0.8 and 0.4 for parent drug, PEMA and PB respectively. Penetration of brain tissue has also been demonstrated with tissue/plasma ratios of about 1 for parent drug and PB. Primidone also crosses the human placenta.

In a group of epileptic children, 92% of the administered dose could be accounted for by parent drug and metabolites in urine, indicating that renal excretion was the major route of elimination and suggesting virtually complete oral bioavailability. In contrast to PB, primidone and PEMA are not bound to plasma proteins to any significant extent.

INDICATIONS:

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.

CONTRAINDICATIONS:

Hypersensitivity or allergic reactions to primidone, acute intermittent porphyria

PRECAUTIONS:

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 is a potent central nervous system depressant and is partially metabolised to phenobarbitone. After prolonged administration there is a potential for tolerance, dependence and a withdrawal reaction on abrupt cessation of treatment.

Primidone, as with other anticonvulsants, can induce liver enzymes and although there is insufficient evidence to suggest a causal relationship, there is a theoretical risk of hepatic damage.

Primidone may also affect Vitamin D metabolism, which may predispose to the development of bone disease. There are reports that long term use may lead to a reduction of bone mineral density and therefore development of osteoporosis (Petty, S.J. *et al*, Neurology, **65**: 1358-1363, 2005). Patients on long term treatment should be monitored for bone density and supplementation with Vitamin D should be considered.

Use in pregnancy (Category D):

The risk of a mother with epilepsy and taking anticonvulsants giving birth to a baby with an abnormality is about three times that of the general population:-

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy. It is, therefore, recommended that:

- *Women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;*
- *AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;*
- *Folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;*
- *Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.*

Withdrawal symptoms may occur in the newborn infant whose mother has received Mysoline during late pregnancy.

Long-term anticonvulsant therapy can be associated with decreased serum folate levels. As folic acid requirements are also increased during pregnancy, regular screening of patients at risk is advised, and treatment with folic acid and cyanocobalamin (vitamin B12), although controversial, should be considered.

The use in pregnancy of primidone, phenobarbitone or methylphenobarbitone has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability.

The use in pregnancy of primidone, alone or in combination with other anticonvulsants, can cause coagulation defects in the newborn infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery. For this reason, pregnant patients should be given phytomenadione (vitamin K1) through the last month of pregnancy up to the time of delivery. In the absence of such pretreatment, phytomenadione 10 mg may be given to the mother at the time of delivery and 1 mg should be given immediately to the neonate.

Use in lactation:

During breastfeeding, the baby should be monitored for sedation.

Effect on ability to drive or operate machinery:

As with most other anticonvulsants, patients who drive vehicles or operate machinery should be aware of the possibility of impaired reaction time.

Interaction:

Both primidone and its major metabolite, phenobarbitone, induce liver enzyme activity. This may lead to altered pharmacokinetics in concomitantly administered drugs including other anticonvulsant drugs, e.g. phenytoin and coumarin anticoagulants.

Breakthrough bleeding and failure of contraceptive therapy have been noted in patients taking anticonvulsant drugs and oral contraceptive steroids. Blood levels of both primidone and any additional anticonvulsant agent may be altered by concomitant administration.

The effects of other CNS depressants (e.g. alcohol and barbiturates) may be enhanced by the administration of primidone.

Suicidal Behaviour and Ideation

Antiepileptic drugs, including primidone, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/ or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5- 100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients events/1000 patients	Relative Risk: Incidence of events in Drug patients/ incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing primidone or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

ADVERSE REACTIONS:

If side effects do appear they are generally confined to the early stages of treatment, when patients frequently feel drowsy and listless.

Visual disturbances, nausea, headache, dizziness, vomiting, nystagmus and ataxia have been reported, but these are usually transient even when pronounced. On occasions, an idiosyncratic reaction may occur which involves these symptoms in an acute and severe form necessitating withdrawal of treatment. Dermatological reactions including severe skin eruptions and, rarely, systemic conditions (e.g. systemic lupus erythematosus) have been reported. Occasional cases of arthralgia and, rarely, personality changes (which may include psychotic reactions) have been reported. As with phenobarbitone, in rare cases Dupuytren's contracture has been reported in patients administered Mysoline.

Exceptionally, as with phenytoin and phenobarbitone, megaloblastic anaemia may develop requiring discontinuation of primidone. This condition may respond to treatment with folic acid and/or cyanocobalamin (vitamin B12). There have been isolated reports of other blood dyscrasias.

DOSAGE AND ADMINISTRATION:

Treatment must always be planned on an individual basis. In many patients, it will be possible to use Mysoline alone, but in some patients, Mysoline will need to be combined with other anticonvulsants.

Mysoline is usually given twice daily. Begin with 1/2 tablet once daily late in the evening. Every three days, increase the daily dosage by 1/2 tablet until the patient is receiving 2 tablets daily. Thereafter, every three days, increase the daily dosage by 1 tablet in adults or 1/2 tablet in children under 9 years, until control is obtained or the maximum tolerated dosage is being given. This may be as much as 6 tablets/day in adults or 4 tablets/day in children. See Table 1.

Table 1: Average daily maintenance doses

Age Group	Tablets	mg
Children up to 2 years	1-2	250-500
Children 2-5 years	2-3	500-750
Children 6-9 years	3-4	750-1,000
Adults, children over 9 years	3-6	750-1,500

The total daily dose is usually best divided and given in two equal amounts, one in the morning and the other in the evening. In certain patients, it may be considered advisable to give a larger dose when the seizures are more frequent. For instance, if the attacks are nocturnal then all or most of the day's dose may be given in the evening; or if the attacks are associated with some particular event such as menstruation, a slight increase in dose at the appropriate time is often beneficial.

Patients taking other anticonvulsants

Where a patient's attacks are not efficiently well controlled with other anticonvulsants, or disturbing side effects have arisen, Mysoline may be used to augment or replace existing treatment. First add Mysoline to the current anticonvulsant treatment by the method of gradual introduction described previously. When a worthwhile effect has been achieved and the amount of Mysoline being given has been built up to at least half the estimated requirement, withdrawal of the previous treatment can then be attempted. This should be done gradually over a period of two weeks, during which time it may be necessary to increase the Mysoline dosage to maintain control. Withdrawal of previous treatment should not be too rapid or status epilepticus may occur. Where phenobarbitone formed the major part of the previous treatment, however, both its withdrawal and Mysoline substitution should be made earlier, so as to prevent excessive drowsiness from interfering with accurate assessment of the optimum dosage of Mysoline.

OVERDOSAGE:

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

Treatment: Treatment should include supportive measures. There is no specific antidote.

Presentation:

Tablets, 250 mg (white, scored, marked M on either side of score), 200's

Shelf Life:

STORAGE: Store below 25 °C. Protect from light and moisture.

SPONSOR:

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Safety Related notification 11th August 2006

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