

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mysoline 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing Primidone 250 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round white, biconvex tablet intagliated on one face and plain on the other.
The scoreline allows the tablet to be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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

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

Mysoline is usually given twice daily. Begin with 125 mg once daily late in the evening. Every three days increase the daily dosage by 125 mg until the patient is receiving 500 mg daily. Thereafter, every three days increase the daily dosage by 250 mg in adults or 125 mg in children under 9 years - until control is obtained or the maximum tolerated dosage is being given. This may be as much as 1,500 mg a day in adults; 1,000 mg a day in children.

Average daily maintenance doses:		
	Tablets (250 mg)	Milligrams
Children up to 2 years	1-2	250 - 500
Children 2-5 years	2-3	500 - 750
Children 6-9	3-4	750 - 1,000
Adults and 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: 1) if the attacks are nocturnal then all or most of the day's dose may be given in the evening; 2) if the attacks are associated with some particular event such as menstruation, a slight increase at the appropriate time is often beneficial.

Patients on other anticonvulsants: Where a patient's attacks are not sufficiently 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 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.

4.3 Contraindications

Patients who are hypersensitive or exhibit an allergic reaction to primidone, to a constituent of the formulation or to phenobarbitone, should not receive the drug.

Mysoline should not be administered to patients with porphyria.

4.4 Special warnings and precautions for use

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

Primidone is a potent CNS 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.

Mysoline 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.

Mysoline may also affect vitamin D metabolism, which may predispose to the development of bone disease. Vitamin D supplementation may be needed during long-term Mysoline therapy.

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 Vitamin B12.

Mysoline has the potential to harm the foetus, see section 4.6 Pregnancy and lactation before considering use during pregnancy.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of anti-epileptic drugs has 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.

4.5 Interaction with other medicinal products and other forms of interaction

Both primidone and its major metabolite, phenobarbitone, induce liver enzyme activity, principally the CYP 450 3A4 enzyme system. This may lead to alteration in the pharmacokinetics of concomitantly administered drugs. Other drugs whose metabolism may be increased and lead to lowered plasma levels and/or a shorter half-life by concomitant Mysoline therapy include:

Androgens, beta-antagonists, carbamazepine, cyclosporin, clozapine, chloramphenicol*, corticosteroids/glucocorticosteroids, cyclophosphamide, dicoumarins, digitoxin, doxycycline, ethosuxamide, etoposide, felbamate*, granisetron, lamotrigine, losartan, methadone, metronidazole*, mianserin, montelukast, nelfinavir*, nimodipine, oral-contraceptives, oxcarbazepine, phenytoin, quinidine, rocuronium, sodium valproate*, tiagabine, theophyllines*, topiramate, tricyclic antidepressants, vecuronium, warfarin and zonisamide.

The following agents also inhibit the CYP 450 3A4 enzyme system and may result in increased plasma levels of concomitantly administered primidone and its metabolite phenobarbitone:

Chloramphenicol*, Felbamate*, nelfinavir*, metronidazole* and sodium valproate*.

St John's Wort induces the enzymes system and may result in a reduction of plasma levels of concomitantly administered primidone and of its metabolite phenobarbitone.

Mysoline inhibits the glucoronidation of paracetamol and may increase the hepatotoxicity of paracetamol.

Theophylline* protein binding may affect phenobarbitone binding, affecting free phenobarbitone levels.

The CNS depressant effect of Mysoline is additive to those of other CNS depressants such as alcohol, opiates and barbiturates.

The above interactions are potentially clinically significant.

*Indicates that the interaction affects both the concomitant agent and Mysoline.

4.6 Fertility, pregnancy and lactation

Pregnancy:

As with other anticonvulsants there is evidence of a teratogenic effect in animal studies. There have been reports of congenital abnormalities, including congenital heart disease, cleft palate and conditions associated with maternal folate deficiency, in infants born of epileptic mothers treated with primidone. This information should be taken into account when considering primidone or alternative managements of epilepsy during pregnancy.

Withdrawal symptoms may occur in the newly born whose mothers have 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 Vitamin B12, although controversial, should be considered.

Anticonvulsant therapy in pregnancy has occasionally been associated with coagulation disorders in the neonate. 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 pre-treatment, 10 mg Vitamin K1 may be given to the mother at the time of delivery, and 1 mg should be given immediately to the neonate.

Lactation:

During breast feeding the baby should be monitored for sedation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

If adverse effects do appear, the most common side effects are drowsiness and listlessness but these generally occur only in the beginning of treatment.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with Mysoline. The mechanism by which Mysoline affects bone metabolism has not been identified.

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.

Common (>1/100)	General	Drowsiness.
	Central and peripheral nervous system	Listlessness, ataxia, visual disturbances, nystagmus.
	Gastrointestinal	Nausea.
Less common (1/100 - 1/1000)	General	Headache, dizziness.
	Gastrointestinal	Vomiting.
	Dermatological	Allergic reactions particularly affecting the skin can include maculopapular, morbilliform or scarlatiniform rashes.
Rare (< 1/1000)	Central and peripheral nervous system	Personality changes, which may include psychotic reactions.
	Haematological	Megaloblastic anaemia, blood dyscrasias.
	Musculoskeletal	Arthralgia, osteomalacia. As with phenobarbitone, Dupuytren’s contracture has been reported.
	Dermatological	Severe reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and lupus erythematosus.

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 Vitamin B12.

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

4.9 Overdose

Primidone is metabolised extensively to phenobarbitone and overdosage leads to various 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).
Therapeutic classification: N03AA03.

The activity of Mysoline is due to the anticonvulsant properties of three active moieties, namely primidone itself and its two major metabolites phenobarbitone and phenylethylmalonamide. The relative contribution of these three moieties to the clinical anticonvulsant effect has not been firmly established. Although the precise mode of action of Mysoline 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.

5.2 Pharmacokinetic properties

Mysoline is absorbed rapidly from the gastrointestinal tract, peak plasma levels being attained approximately 3 hours after ingestion. Primidone is well distributed in all organs and tissues: it crosses the blood-brain and placental barriers and is excreted in breast milk. The pharmacokinetics of primidone are complex because of biotransformation into two metabolites, phenobarbitone and phenylethylmalonamide, that have anticonvulsant activity and complex pharmacokinetic properties. Primidone has a plasma half-life of approximately 10 hours which is considerably shorter than those of its principal metabolites. Primidone and phenylethylmalonamide are bound to plasma proteins to only a small extent, whereas approximately half of phenobarbitone is bound. Approximately 40% of the drug is excreted unchanged in urine.

5.3 Preclinical safety data

Primidone is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Gelatin
Carmellose calcium
Magnesium stearate
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. In order to protect from light and moisture, keep the bottle in the outer carton and tightly closed.

6.5 Nature and contents of container

HDPE bottle (100 tablets).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoires SERB
40 avenue George V
75008 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA 1777/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

September 2012