

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

'Mysoline'

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Primidone Ph. Eur. 250 mg

3. PHARMACEUTICAL FORM

White uncoated oral tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

'Mysoline' 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

Epilepsy: 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 or with supporting therapy.

'Mysoline' is usually given twice daily. Begin with 125 mg once daily late in the evening. Every 3 days increase the daily dosage by 125 mg until the patient is receiving 500 mg daily. Thereafter, every 3 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 1.5 g a day in adults; 1 g a day in children.

Average daily maintenance doses:

	Tablets (250mg)	Milligrams
Adults and children over 9 years	3 to 6	750 to 1500
Children 6 to 9 years	3 to 4	750 to 1000
Children 2 to 5 years	2 to 3	500 to 750
Children up to 2 years	1 to 2	250 to 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 in the appropriate dose is often beneficial.

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

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 2 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'.

Essential tremor: Initially a dose of 50 mg daily should be introduced using 'Mysoline' Suspension. The daily dose 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 750 mg daily.

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 tolerance to 'Mysoline', frequently characterised by vertigo, unsteadiness and nausea. It is, therefore, essential to start such patients at a low dosage (initially 50 mg daily) increasing very slowly up to the maximum tolerated dose or that which produces remission of tremor (up to 750mg daily).

4.3 Contraindications

Patients who exhibit hypersensitivity or an allergic reaction to primidone, to a constituent of the formulation or to phenobarbitone, should not receive the drug. Primidone should not be administered to patients with acute intermittent porphyria.

4.4 Special Warnings and Special Precautions for Use

'Mysoline' 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 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.

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. There have been isolated reports of other blood dyscrasias.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Both primidone and its major metabolite phenobarbitone induce liver enzyme activity. This may lead to altered pharmacokinetics in concomitantly administered drugs including other anticonvulsants such as phenytoin and coumarin anticoagulants. Blood levels of both 'Mysoline' and any additional anticonvulsant agent may be altered by concomitant administration.

Breakthrough bleeding and failure of contraceptive therapy have been noted in patients taking anticonvulsant drugs and oral contraceptive steroids. This is usually assumed to be due to induction of liver enzymes by the anticonvulsant with accelerated breakdown of the hormones.

The effects of other CNS depressants such as alcohol and barbiturates may be enhanced by the administration of 'Mysoline'. St John's Wort (*Hypericum perforatum*) may decrease plasma concentration of primidone resulting in reduced therapeutic effect.

4.6 Pregnancy and Lactation

Pregnancy: There is some evidence of a higher than average incidence of congenital abnormalities in infants born of epileptic mothers. The factors influencing this are unknown, but the possibility that anticonvulsant therapy may be involved and the very slight risk of an abnormal foetus must be weighed against the risk of withholding treatment 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 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, 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 at risk.

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.

Visual disturbances, nausea, headache, dizziness, vomiting, nystagmus and ataxia have been reported but 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

	Hepatic	Elevations in hepatic enzymes, including gamma-glutamyl transferase (gamma GT) and alkaline phosphatase.
	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.

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

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.

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

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.

'Mysoline', as with other anticonvulsants, can induce liver enzymes.

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 Pre-clinical 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

Carmellose calcium Ph. Eur.
Gelatin Ph. Eur.
Magnesium stearate Ph. Eur.
Povidone Ph. Eur.
Purified water Ph. Eur.
Stearic acid Ph. Eur.

6.2 Incompatibilities

None known.

6.3 Shelf Life

5 years.

6.4 Special Precautions for Storage

Store below 25°C.

6.5 Nature and Contents of Containers

HDPE bottle (100 tablets).

6.6 Instructions for Use/Handling

To be taken as directed by the prescriber.

7. MARKETING AUTHORISATION HOLDER

Acorus Therapeutics Limited
High Crane Lodge
Hamsterley
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Durham
DL13 3QS

8. MARKETING AUTHORISATION NUMBER

PL 20132/0005

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

14 August 2004

10. DATE OF (PARTIAL) REVISION OF THE TEXT

31 July 2006