PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM

MYSOLINE Tablets

COMPOSITION

Each **MYSOLINE** tablet contains 250 mg primidone.

List of Excipients: Carmellose calcium, gelatine, magnesium stearate, povidone, stearic acid.

Sugar free.

CATEGORY AND CLASS

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The activity of primidone 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 primidone is unknown, effects on the neuronal membrane particularly with respect to alteration of ionic fluxes are likely to play a fundamental role.

Pharmacokinetic properties

Primidone is usually absorbed rapidly from the gastro-intestinal tract with wide individual variation. Peak plasma levels are 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. Primidone has a plasma half-life of 7 to 14 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 medicine is excreted unchanged in urine.

INDICATIONS

MYSOLINE is indicated for treatment of epilepsy for:

- Generalised tonic-clonic seizures
- Partial seizures with or without secondary generalisation (temporal lobe seizures; focal seizures)

It is also effective in the control of myoclonic jerks and akinetic attacks.

CONTRAINDICATIONS

Patients who exhibit hypersensitivity or allergic reactions to primidone or any other ingredient of **MYSOLINE**. **MYSOLINE** should not be administered to patients with acute intermittent porphyria.

Concomitant use of **MYSOLINE** and phenobarbitone is contraindicated, except when transferring treatment from one to the other (see **WARNINGS**).

Patients with severe hepatic, renal or respiratory impaired function.

Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS and SPECIAL PRECAUTIONS

MYSOLINE has the potential to harm the foetus (refer to **PREGNANCY AND LACTATION** section).

Suicidal ideation and behaviour have been reported in patients treated with **MYSOLINE**. Patients taking **MYSOLINE** 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.

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

MYSOLINE is a potent central nervous system (CNS) depressant and is metabolised to phenobarbitone, therefore the combination of both agents is contraindicated. However, if patients are to be transferred from phenobarbitone to **MYSOLINE**, then it is recommended that the withdrawal of phenobarbitone 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. After prolonged administration there is a potential for tolerance, dependence and a withdrawal reaction on abrupt cessation 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 bones metabolism has not been identified.

Driving and using machinery:

Patients who drive vehicles or operate machinery should be aware of the possibility of impaired reaction time.

INTERACTIONS

Both **MYSOLINE** and its major metabolite, phenobarbitone, induce liver enzyme activity, principally the CYP450 3A4 enzyme system. This may lead to alteration in the pharmacokinetics of concomitantly administered medicines. Other medicines whose metabolism may be increased and lead to lowered plasma levels and/or shorter half-life by concomitant **MYSOLINE** therapy include: Androgens, beta-antagonists, carbamazepine, cyclosporin, clozapine, chloramphenicol*, corticosteroids/ glucocorticoids, cyclosphosphamide, digoxin, 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.

Breakthrough bleeding and failure of contraceptive therapy have been noted in patients taking anticonvulsant medicines and oral contraceptive steroids.

The following agents also inhibit the CYP450 3A4 enzyme system and may result in increased plasma levels of concomitantly administered **MYSOLINE** and its metabolite

phenobarbitone: Chloramphenicol*, felbamate*, nelfinavir*, metronidazole* and sodium valproate*.

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

MYSOLINE inhibits the glucuronidation of paracetamol and may increase the hepatotoxicity of paracetamol.

Theophylline* protein binding may affect phenobarbitone binding, the major metabolite of **MYSOLINE**, 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**.

HUMAN REPORDUCTION

Pregnancy

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. **MYSOLINE** is not recommended during pregnancy. (See **WARNINGS**).

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

Long-term **MYSOLINE** 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 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 K_1 through the last month of pregnancy up to the time of delivery. In the absence of such pre-treatment, 10 mg Vitamin K_1 may be given to the mother at the time of delivery and 1 mg should be given immediately to the neonate.

Lactation

Breastfeeding is not recommended.

DOSAGE AND DIRECTIONS FOR USE

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.

When **MYSOLINE** is used with or to replace existing anticonvulsant therapy, the dosage should be increased gradually while that of the other medication is maintained or decreased gradually in order to maintain seizure control. This should be done over a period of two weeks.

MYSOLINE is usually given twice daily. Begin with half a tablet once daily late in the evening. Every three days increase the daily dosage by half a tablet until the patient is receiving 2 tablets daily. Thereafter, every three days increase the daily dosage by one tablet in adults or half a 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 a day in adults; 4 tablets a day in children.

Average daily maintenance doses:

	Tablets	mg
Children up to 2 years	1 to 2	250 to 500
Children 2 to 5 years	2 to 3	500 to 750
Children 6 to 9 years	3 to 4	750 to 1 000
Adults and children over 9 years	3 to 6	750 to 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.

SIDE-EFFECTS

The most common side effects are drowsiness and listlessness.

Common: ≥ 1/100, < 1/10

Uncommon: ≥ 1/1000, < 1/100

Rare: ≥ 1/10 000, < 1/1000

Nervous system disorders

Common: Listlessness, ataxia, visual disturbances, nystagmus.

Gastrointestinal disorders

Common: Nausea.

Uncommon: Vomiting.

Skin disorders

Uncommon: Allergic reactions particularly affecting the skin can include maculopapular, morbilliform or scarlatiniform rashes.

Rare: Severe skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and lupus erythematosus.

Psychiatric disorders

Rare: Personality changes, which may include psychotic reactions.

Blood disorders

Rare: Megaloblastic anaemia, blood dyscrasias.

Hepato-biliary disorders

Rare: Elevations in hepatic enzymes, including Gamma-GT and alkaline phosphatase.

Musculoskeletal disorders

Rare: Arthralgia, osteomalacia. Dupuytren's contracture has been reported.

Renal disorders

Uncommon: Polyuria.

Reproductive system disorders

Uncommon: Impairment of sexual function.

General disorders

Common: Drowsiness.

Uncommon: Headache, dizziness, oedema of the legs, thirst

Visual disturbances, headache, dizziness, nystagmus, ataxia, vomiting and nausea are usually transient when pronounced. An idiosyncratic reaction may occur which involves these symptoms in an acute and severe form necessitating withdrawal of treatment.

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

Megaloblastic anaemia may develop requiring discontinuation of **MYSOLINE**. This condition may respond to treatment with folic acid and/or Vitamin B_{12}.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Primidone is metabolised 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 **MYSOLINE** overdosage is suspected.

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

There is no specific antidote.

IDENTIFICATION

MYSOLINE tablets are round, white to almost white, biconvex, uncoated tablets, bisected on one side with 'M' impressed on either side of the breakline.

PRESENTATION

MYSOLINE tablets is supplied in a white high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure or a white polyvinyl chloride (PVC) / aluminium foil blister pack containing 100 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

MYSOLINE tablets: B/2.5/572

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

MIDRAND

DATE OF PUBLICATION OF THIS PROFESSIONAL INFORMATION

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