Mysoline 50mg Tablets

(primidone)

PL 20132/0006

UK Public Assessment Report

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Mysoline 50mg Tablets

(primidone)

PL 20132/0006

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Acorus Therapeutics Limited a Marketing Authorisation (licence) for the medicinal product Mysoline 50mg Tablets (PL 20132/0006) on 2nd June 2010. This is a prescription-only medicine (POM).

Mysoline 50mg Tablets contain the active ingredient primidone, which belongs to a group of medicines used to treat seizures. This product is used for the treatment of certain types of epilepsy, seizures (fits) or shaking attacks (essential tremor).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Mysoline 50mg Tablets, for the conditions described in the attached Summary of Product Characteristics (SmPC), outweigh the risks; hence a Marketing Authorisation (MA) has been granted.

Mysoline 50mg Tablets

(primidone)

PL 20132/0006

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Acorus Therapeutics Limited a Marketing Authorisation for the medicinal product Mysoline 50mg Tablets (PL 20132/0006) on 2nd June 2010. The product is a prescription-only medicine (POM).

This is an abridged application for Mysoline 50mg Tablets, submitted under Article 8.3 of 2001/83 EC, as amended, as a line extension to Mysoline 250 mg Tablets (PL 20132/0005), authorised to Acorus Therapeutics Limited on 14th August 2004. Mysoline 250 mg Tablets contain the 'known active substance' primidone and have a well established use in the management certain types of epilepsy and essential tremor.

Mysoline 50mg Tablets are indicated in the management of grand mal and psychomotor (temporal lobe) epilepsy. They are also of value in the management of focal or Jacksonian seizures, myoclonic jerks and akinetic attacks. This medicinal product is also used for the management of essential tremor. The proposed indications and posology are identical to those currently approved for the existing product. The 50 mg presentation is aimed at facilitating dose titration, particularly in the initial treatment of essential tremor, where a starting dose of 50 mg daily is prescribed, rather than epilepsy, where the starting dose is 125 mg. The necessity for this new strength has arisen through the discontinuation of 'Mysoline Suspension'.

The active ingredient primidone belongs to the pharmacotherapeutic group, antiepileptics (ATC code - N03A A03). The activity of Mysoline 50mg Tablets 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, 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.

Primidone 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.

No new pre-clinical or clinical efficacy studies were conducted or required for this application. Bioequivalence studies are not necessary to support this application for a line extension of an existing product, with the same manufacturer and manufacturing method.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a detailed Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a line extension of an approved product and it is not likely to change the total market of primidone. As the application is for a line extension with the same clinical indications as an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

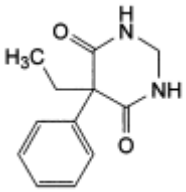
Primidone

Nomenclature:

INN: Primidone

Chemical names: 5-Ethyl-5-phenyldihydropyrimidine-4,6(1*H*,5*H*)-dione

Structure:



Molecular formula: $C_{12}H_{14}N_2O_2$

Molecular weight: 218.3 g/mol

CAS No: 125-33-7

Physical form: A white or almost white crystalline powder.

Solubility: Very slightly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in ether. It dissolves in alkaline solutions.

The active substance, primidone, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of primidone are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of primidone for inclusion in this medicinal product.

The active substance is stored in appropriate packaging. The primary packaging is polyethylene bags, which are sealed and placed into cardboard drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been presented for the active substance stored in packaging representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and no significant changes in active substance quality were observed. The proposed retest period of 48 months, when stored at or below 25°C, is justified.

MEDICINAL PRODUCT

Description and Composition

The medicine is presented as a white or virtually white, round, biconvex, uncoated tablet with an 'M' on one side. Each tablet contains 50mg of the active substance, primidone.

Other ingredients consist of pharmaceutical excipients, namely carmellose calcium, gelatin, magnesium stearate, povidone K30, purified water and stearic acid. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

Satisfactory declarations are provided by the suppliers of magnesium stearate and stearic acid confirming that these materials are not of animal origin. A satisfactory TSE Certificate of Suitability has been provided for gelatin stating that it meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory.

The rationale behind the development of the 50 mg strength is that initial dose titration, fine adjustment and controlled treatment withdrawal is not straightforward with a single tablet strength of 250 mg. The 50 mg tablets are a proportional scale-down of the approved 250 mg strength formulation; they are to be manufactured at the same site, and by the same process, as the approved product. Compatibility between active substance and excipients is, therefore, long-established. Comparable dissolution behaviour has been demonstrated between the 250 mg tablets and 5 x 50 mg tablets.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data were provided for 3 commercial scale batches and all data were within specification. Critical stages of the manufacturing process have been evaluated, and the process and controls demonstrated as capable of consistently yielding product of the required quality.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been

described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for three production scale batches of the product; they demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in HDPE bottles containing 100 tablets, with white HDPE, tamper-evident, child resistant push-on caps. These HDPE bottles are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The HDPE bottles comply with EU legislation, Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 5 years has been set, which is satisfactory. Storage instructions are ‘Store below 25°C.’.

Bioequivalence Study

This application is a line extension of an approved originator product. The ‘new’ 50 mg strength is qualitatively identical to the approved 250 mg product and the formulation is scaled down proportionally. The same manufacturer and manufacturing method are used. Comparable dissolution behaviour has been demonstrated between the 250 mg tablets and 5 x 50 mg tablets. Therefore, it is not considered necessary for a bioequivalence study to be carried out.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

This application is a line extension of the approved originator product, Mysoline 250 mg Tablets (PL 20132/0005). The test product, Mysoline 50 mg Tablets, is qualitatively identical to the approved 250 mg strength product and the formulation is scaled down proportionally. The same manufacturer and manufacturing method are used. A bioequivalence study was not necessary to support this application.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.

PRE-CLINICAL ASSESSMENT

This is an abridged application for Mysoline 50mg Tablets, submitted under Article 8.3 of 2001/83 EC, as amended, as a line extension to Mysoline 250 mg Tablets (PL 20132/0005, Acorus Therapeutics Limited). Mysoline 250 mg Tablets contain the 'known active substance' primidone and have a well established use in the management certain types of epilepsy and essential tremor.

No new pre-clinical data have been supplied with this application and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified expert and is satisfactory. The CV of the expert has been supplied.

CLINICAL ASSESSMENT

BACKGROUND

This is a national abridged application for Mysoline 50 mg Tablets, developed by the applicant as a line extension to Mysoline 250 mg Tablets (PL 20132/0005), which have a well established use in the management of epilepsy and essential tremor. The active ingredient, primidone, has been used as a treatment for various forms of epilepsy for over 50 years.

The dosing requirements of primidone approved for the 250mg product justify the need for a 50mg dose, this lower dosing unit of primidone assisting in the dose titration. Mysoline 50 mg Tablets contain the same active ingredient (primidone) and are manufactured to the same relative composition as Mysoline 250 mg Tablets.

INDICATIONS

Mysoline 50mg Tablets are indicated in the management of grand mal and psychomotor (temporal lobe) epilepsy. They are also of value in the management of focal or Jacksonian seizures, myoclonic jerks and akinetic attacks. This medicinal product is also used for the management of essential tremor.

The proposed indications are identical to those currently approved for Mysoline 250 mg Tablets.

POSOLOGY AND METHOD OF ADMINISTRATION

The proposed posology is identical to that currently approved for the existing product, Mysoline 250 mg Tablets. The 50 mg presentation is aimed at facilitating dose titration, particularly in the initial treatment of essential tremor, where a starting dose of 50 mg daily is prescribed, rather than epilepsy, where the starting dose is 125 mg. The necessity for this new strength has arisen through the discontinuation of ‘Mysoline Suspension’. Full details concerning the posology are provided in the SmPC.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of primidone is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

This application is a line extension of an approved product. Mysoline 50mg Tablets are qualitatively identical to the approved 250 mg product and the formulation is scaled down proportionally. The same manufacturer and manufacturing method are used. Data are presented confirming high solubility and linearity of kinetics over the therapeutic range. It is not, therefore, considered necessary for a bioequivalence study to be carried out and a biowaiver was accepted.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of primidone is well-established from its extensive use in clinical practice.

SAFETY

No novel safety data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of primidone is well-known.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the originator product, and is acceptable.

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

DISCUSSION AND CONCLUSION

All issues have been adequately addressed by the applicant. The product literature is approved. Sufficient clinical information has been submitted to support this application. When used as indicated, Mysoline 50mg Tablets has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was therefore recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Mysoline 50mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

No new pre-clinical data were submitted and none are required for an application of this type.

EFFICACY

The efficacy of primidone is well-established from its extensive use in clinical practice. Primidone has been used as a treatment for various forms of epilepsy for over 50 years.

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new pre-clinical or clinical safety concerns have been identified. This application is a line extension of Mysoline 250 mg Tablets (PL 20132/0005). Mysoline 50 mg Tablets are qualitatively identical to the approved 250 mg strength product and the formulation is scaled down proportionally. The same manufacturer and manufacturing method are used. A bioequivalence study was not required to support this application. Extensive clinical experience with primidone is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

Mysoline 50mg Tablets

(primidone)

PL 20132/0006

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 2nd September 2009

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 14th October 2009

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 26th October 2009 and further information relating to the clinical dossier on 28th October 2009

4 The applicant responded to the MHRA's requests, providing further information for the quality and clinical sections on 11th January 2010

5 Following assessment of the response the MHRA requested further information relating to the quality sections on 24th March 2010

6 The applicant responded to the MHRA's request, providing further information for the quality sections on 15th April 2010

7 The application was determined on 2nd June 2010

Mysoline 50mg Tablets

(primidone)

PL 20132/0006

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Mysoline 50mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Mysoline 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg primidone.

For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White or virtually white, round, biconvex, uncoated tablets intagliated with a single M on one side and plain on the reverse.

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 and may be administered using either the 50 mg or 250 mg strength tablets.

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:

	Milligrams
Adults and 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

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. 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 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.

Primidone has the potential to harm the foetus, see section 4.6 before considering use during pregnancy.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Both primidone and its major metabolite phenobarbitone are metabolized by, and also induce, liver enzyme activity, principally the CYP 450 3A4 enzyme system.

Agents which inhibit the CYP 450 3A4 enzyme system, such as chloramphenicol, felbamate, nelfinavir*, metronidazole and sodium valproate may result in increased plasma levels of concomitantly administered primidone and its metabolite phenobarbitone.

In addition, St. John's Wort* induces the CYP450 enzyme system and may result in a reduction of plasma levels of concomitantly administered primidone and of its major metabolite phenobarbitone.

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

Primidone therapy may also lead to altered pharmacokinetics in concomitantly administered drugs, whose metabolism may be increased and lead to lowered plasma levels and/or a shorter half-life. These drugs include androgens*, beta-antagonists, carbamazepine, cyclosporin, cloazepine, chloramphenicol, corticosteroids/glucocorticosteroids, cyclophosphamide, dicoumarins, digitoxin*, doxycycline, ethosuxamide, etoposide, felbamate, granisetron, lamotrigine, losartan, methadone*, metronidazole, mainserin, montelukast*, nelfinavir*, nimodipine, oral-contraceptives, oxcarbazepine, phenytoin, quinidine, rocuronium, sodium valproate, tiagabine, theophyllines, topiramate, tricyclic antidepressants, vecuronium, warfarin and zonisamide.

Primidone inhibits the glucoronidation of paracetamol* and may increase the hepatotoxicity of paracetamol.

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

The above interactions are potentially clinically significant.

* No formal interaction studies have been performed. The inclusion of the drug is based on reports of their influence or dependence upon enzyme systems influenced by, or of relevance to the metabolic pathways of primidone or its major metabolite, phenobarbitone.

4.6 Pregnancy and lactation

Pregnancy: Primidone is suspected to have caused serious birth defects when administered during pregnancy. In infants born of epileptic mothers treated with primidone, there have been reports of congenital abnormalities including congenital heart disease, cleft palate and conditions associated with maternal folate deficiency, including spina bifida, microencephaly and anencephaly. Primidone should not be used during pregnancy unless clearly necessary to manage epilepsy in the mother where withdrawal of therapy may cause risks or where alternative anti-epileptic managements are unsuitable.

Withdrawal symptoms may occur in the newly born whose mothers have received primidone 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 primidone 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

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 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

Primidone 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

Carmellose calcium
Gelatin
Magnesium stearate
Povidone K30
Purified water
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

HDPE bottle containing 100 tablets, with a white HDPE, tamper-evident, child resistant push-on cap with a white LDPE liner.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Acorus Therapeutics Limited
Office Village
Chester Business Park
Chester
Cheshire
CH4 9QZ.
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20132/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/06/2010

10 DATE OF REVISION OF THE TEXT

02/06/2010

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Mysoline 50 mg and 250 mg Tablets (Primidone)

Read all of this leaflet carefully before you start using this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
In this leaflet:

1. WHAT MYSOLINE IS AND WHAT IT IS USED FOR

Mysoline contains primidone as the active ingredient; this belongs to a group of medicines used to treat seizures.
Mysoline is used for the treatment of certain types of epilepsy, seizures (fits) or shaking attacks (essential tremor).

2. BEFORE YOU USE MYSOLINE

Do not take Mysoline if you:

- are allergic (hypersensitive) to primidone, a substance called phenobarbitone, or to any of the other ingredients of Mysoline (these are listed in Section 6: Further information).
- have porphyria (a rare inherited disorder of metabolism) or anyone in your family has it.

Take special care with Mysoline if you:

- have ever had problems with your breathing, kidneys or liver.
- are pregnant or are trying to become pregnant (see beneath for further information)

If you go into hospital, tell the medical staff that you are taking Mysoline.
A small number of people being treated with anti-epileptics such as primidone have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is important because some medicines may affect the way Mysoline works, or Mysoline may affect the way other medicines work.

In particular, tell your doctor if you are taking any of the following:

- Other medicines used to treat epilepsy and other types of seizures (such as phenytoin, felbamate, sodium valproate, carbamazepine, ethosuxamide, oxcarbazepine, tiagabine, topiramate, zonisamide)
- Anticoagulants to prevent blood clots (such as warfarin)
- Barbiturates (such as sleeping tablets)
- Methadone (used to treat severe pain, cough, or as a substitute for morphine addiction)
- Herbal remedies containing St Johnís Wort
- Antibiotics (such as chloramphenicol, metronidazole, doxycycline)
- Antiviral medicines (such as nelfinavir)
- Asthma medicines (such as theophylline, montelukast)
- Hormone containing medicines (such as the oral contraceptive pill)
- Medicines used to treat high blood pressure or heart conditions (such as beta-blockers, digitoxin, losartan, nimodipine, quinidine)
- Cyclosporin (used to prevent rejection of an organ transplant and also for other diseases of the bodyís immune system)
- Medicines used to treat mental health problems or depression (such as cloazepine, lamotrigine, mianserin, tricyclic antidepressants)
- Steroid-containing medicines
- Medicines used to treat cancer (such as cyclophosphamide, etoposide)
- Granisetron (used to treat severe nausea and vomiting)
- Medicines used during an anesthetic for surgery (such as rocuronium, vecuronium)
- Medicines containing morphine, or similar medicines called opiates

Mysoline may increase the toxic effect on the liver of an overdose of paracetamol.

Taking Mysoline with food and drink

Alcohol can react with Mysoline. Ask your doctor for advice if you want to drink alcohol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

The use of Mysoline in pregnancy is associated with an increased risk of abnormalities in babies. Therefore, you must tell your doctor if you are pregnant, or trying to become pregnant because Mysoline has the potential to harm your unborn child.

Pregnant women can have reduced folic acid in their blood whilst taking Mysoline. In addition, the new born child may develop withdrawal symptoms if the mother has taken Mysoline in the late stages of pregnancy. Blood clotting problems have occurred occasionally in children born to women who were previously taking anticonvulsant drugs. Tell your doctor if you are breast-feeding because Mysoline may cause your baby to be very sleepy.

Driving and using machines

Mysoline can make you feel sleepy. If so, do not drive or operate machinery.

3. HOW TO USE MYSOLINE

Always take Mysoline exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the tablets whole with a drink of water.

Mysoline is normally taken twice a day. Try to take your tablets at the same time each day.

Epilepsy

At first, your dose may be as little as 125 mg (half a 250 mg tablet). This will be adjusted by your doctor until your condition is controlled. Typical maintenance doses are as follows:

Age group	Daily dose (milligrams)
Adults and 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

Elderly / Patients with low physical strength

Lower doses may be prescribed.

Shaking attacks (essential tremor)

Your starting dose may be 50 mg. This will be adjusted by your doctor until your condition is controlled.

The maximum daily dose for shaking attacks (essential tremor) is 750 mg.

If you take more Mysoline than you should

If you take more than your normal dose, contact your doctor or nearest hospital.

If you forget to take Mysoline

If you miss a dose, take it as soon as you remember. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Mysoline

Do not stop taking your Mysoline, even if you are feeling well, unless your doctor tells you to. You may have become dependent on Mysoline, and therefore you could get a withdrawal reaction if you stop treatment too quickly. Mysoline treatment should be reduced gradually to prevent this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Mysoline can cause side effects, although not everybody gets them.

When first taking Mysoline, drowsiness and lack of energy may occur; these usually pass.

Common side effects (affecting fewer than 1 in every 10 people)

- disturbances of vision
- dizziness
- jerky movements
- rolling of the eyes

Uncommon side effects (affecting fewer than 1 in every 100 people)

- nausea and vomiting
- headache
- skin rash

Rare side effects (affecting fewer than 1 in every 1000 people)

- joint or bone pain

- changes in mood or behaviour.
- severe skin reactions affecting large portions of your body including redness, pain, ulcers, blisters, shedding the outer layer of skin or involvement of lips or the lining of the mouth, nostrils or ears (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome),
- a disease called lupus erythematosus which causes inflammation of various parts of the body including the skin, joints, lungs, kidneys, heart, and liver.
- development of Dupuytren's contracture (a thickening of fibrous tissue in the palm of the hand that causes one or more fingers to draw back).
- abnormalities of the blood cells; if you notice a pale appearance of your skin, abnormal bleeding or tendency to bruising, fever or sore throat please consult your doctor.
- raised levels of enzymes in your liver.

Do not be alarmed by this list of possible events. You may not have any of them.

If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MYSOLINE

Keep out of the reach and sight of children

Keep your tablets below 25°C.

Do not use Mysoline after the expiry date which is stated on the carton as {EXP MM/YYYY}. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Mysoline contains

The active substance is primidone. Each tablet contains 50 mg. The other ingredients are carmellose calcium, gelatin, magnesium stearate, povidone K30 and stearic acid, which are all typical ingredients used in tablet manufacture.

What Mysoline looks like and contents of the pack

Mysoline 50 mg Tablets are white uncoated tablets for oral use. One side of the tablet has a single letter 'M'. The other side of the tablet is plain.

Mysoline 250 mg Tablets are white uncoated tablets for oral use. One side of the tablet has the letter 'M' each side of a break-line. The other side of the tablet is plain.

Mysoline comes in containers of 100 tablets.

Marketing Authorisation Holder

Acorus Therapeutics Limited, Office Village, Chester Business Park, Chester, Cheshire, CH4 9QZ, UK

Manufacturer

Recipharm Limited, Vale of Bardsley, Ashton-under-Lyne, Lancashire, OL7 9RR, UK.

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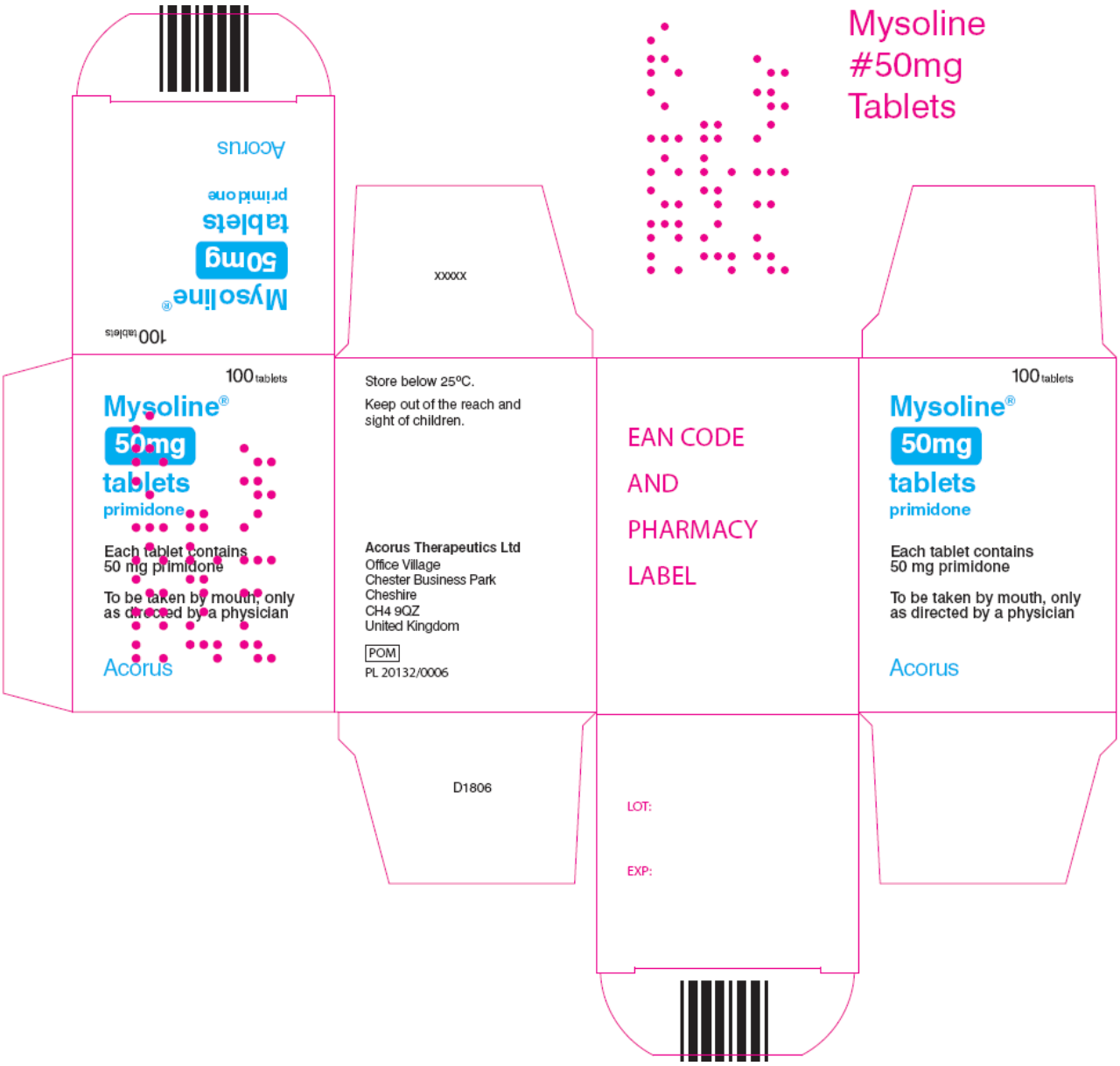
Is this leaflet hard to see or read? Phone 0800 198 5000 for help.

LABELLING

Carton for HDPE bottle, with braille



HDPE bottle label