Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mysoline 250mg 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 tablet can be divided into equal doses.

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.

4.2 Posology and method of administration

Posology
Treatment should always be planned on an individual basis. In many patients, primidone treatment may be given as monotherapy, but in some it is necessary to give Mysoline in combination with other anticonvulsants or with supporting therapy.

Primidone should be started with the lowest possible dose, in the evening, in order to minimise neurological and digestive adverse reactions that can occur within the first few weeks of treatment. If this first dose is well tolerated, the daily dose should be given in two equal doses, one in the morning and the other in the evening, to ensure that serum primidone remains above therapeutic levels throughout the day.

In certain patients, it may be advisable to give a larger dose when seizures are more frequent. For instance:
1) If seizures occur at night, then all or most of the daily dose may be given in the evening;
2) If seizures are associated with a particular event such as menstruation, a slight increase in the dose around the event is often beneficial.

- In adults:

Initial dose: The initial dose is usually 125 mg in a single dose in the evening. Then every 3 days, the daily dose is increased by 125 mg until the patient is receiving 500 mg daily. Then, every 3 days, the daily dose is increased by 250 mg until control of the situation is achieved or until the maximum tolerated dose is reached. The daily dose may be up to 1.5 g.

Maintenance dose:

	Tablets (250 mg)	**Milligrams**
Adults	3 - 6	750 - 1500

- Paediatric population:

Initial dose: This initial dose is usually 125 mg in a single dose in the evening. Then every 3 days, the daily dose is increased by 125 mg until the patient is receiving 500 mg daily. Then, every 3 days, the daily dose is increased by 125 mg until control of the daily dose is achieved or until the maximum tolerated dose in children is reached.

Maintenance doses:

	Tablets (250mg)	**Milligrams**
Children up to 2 years	1 - 2	250 - 500
Children 2-5 years	2 - 3	500 - 750
Children 6-9 years	3 - 4	750 - 1000
children over 9 years	3 - 6	750 - 1500

Special populations:

Patients with renal impairment
Due to decreased renal elimination of primidone in patients with renal insufficiency, the dose should be adjusted according to clinical response and monitoring of laboratory parameters.

Patients with hepatic impairment
Due to decreased hepatic metabolism of primidone in patients with severe hepatic impairment, the dose should be adjusted according to clinical response and monitoring of laboratory parameters.

Concomitant use / switch from other anticonvulsant treatments
If other anticonvulsant treatments are ineffective or if these drugs induce adverse reactions, primidone may be used to increase the efficacy of the existing/underlying treatment or as a replacement therapy. Primidone should initially be added to the previous treatment according to a progressive dose increase method as described above. 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 be attempted. This dose adjustment should be performed progressively over a period of 2 weeks during which primidone dose increase could be necessary in order to maintain good control of the patient's condition.

The previous treatment should not be withdrawn too quickly, or else status epilepticus may occur. In cases where phenobarbital was the main component of the previous treatment, it should be withdrawn and substituted with Mysoline more quickly, so as to prevent excessive drowsiness from interfering with the accurate assessment of the optimal dosage of Mysoline

Method of administration
Oral use.
The tablets should be swallowed whole with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance (primidone), to phenobarbital or to any of the excipients listed in section 6.1
- Acute intermittent porphyria

Due to its inducing properties with CYP450, the combination with the following classes of medicinal products is contraindicated:

- certain antivirals (cobicistat, daclatasvir, dasabuvir, ledipasvir, nelfinavir, ombitasvir + paritaprevir, rilpivirine, telaprevir, sofosbuvir) (see section 4.5)
- certain antifungals (voriconazole, isavuconazole) (see section 4.5)
- miscellaneous: lurasidone, delamanid, cholic acid, St. John's wort (see section 4.5)

4.4 Special warnings and precautions for use

Special warnings
Primidone is not effective for the treatment of absences and myoclonic fits, which may be sometimes aggravated by the use of this drug.

Due to its sedative effect, it is recommended that primidone treatment be initiated with the lowest dose in the evening, and then with a stepwise approach (see section 4.2).

Primidone should be administered with caution, and it may be necessary to reduce the dosage in children, the elderly, debilitated (weakened) patients or patients with impaired renal, hepatic or respiratory function.

Primidone may have adverse effects on the foetus (see section 4.6).

Seizure aggravation

Introduction of an antiepileptic drug may, in rare cases, be followed by recurrence of the seizures or by the occurrence of a new type of seizure for the patient, independently of the fluctuations observed in some forms of epilepsy. For primidone, causes of these aggravations may be: a choice of a treatment that is unsuitable for this patient's seizures or epileptic syndrome, a change of the concomitant antiepileptic treatment or a pharmacokinetic interaction, toxicity or overdose. Other causes of seizure aggravation should be excluded before a paradoxical reaction is diagnosed.

Treatment discontinuation

Sudden withdrawal of treatment at effective antiepileptic doses may cause convulsive fits and status epilepticus, mainly in case of concomitant alcohol intake.

Primidone is a potent CNS depressant and is metabolised into phenobarbital, with a highly variable rate depending on the patient. After long-term administration, there is a potential for tolerance, dependence and a withdrawal reaction upon abrupt treatment discontinuation.

Prevention of vitamin deficiencies

Primidone is an enzyme inducer (CYP450) which may increase the catabolism of vitamin D. A dose-dependent increase in the risk of osteomalacia has been observed during primidone therapy, which may predispose patients to developing bone disease. Vitamin D supplementation may be needed during long-term primidone therapy (see section 4.8).

Exceptionally, as with phenytoin and phenobarbital, megaloblastic anaemia may develop and require discontinuation of primidone. This condition may respond to treatment with folic acid and/or vitamin B12 (see section 4.8).

Suicidal behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic drugs has also shown a slightly increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not rule out the possibility of an increased risk with primidone.

Patients should therefore be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and their caregivers) should be advised to seek medical advice if signs of suicidal ideation or behaviour appear.

Severe skin reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of primidone.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

The highest risk for occurrence of SJS, TEN or DRESS is within the first weeks of treatment.

If symptoms or signs of SJS, TEN or DRESS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, primidone treatment should be discontinued.

The best results in managing SJS, TEN and **DRESS** come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS, TEN or DRESS with the use of primidone (or phenobarbital), primidone must not be re-started in this patient at any time (see section 4.8).

Women of childbearing potential

Primidone is extensively metabolised to phenobarbital. Thus information on phenobarbital must be taken into account.

Phenobarbital may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenobarbital may increase the risk for congenital malformations approximately 2- to 3-fold (see section 4.6).

Primidone should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options. Women of childbearing potential should be fully informed of the potential risk to the foetus if they take primidone during pregnancy.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with primidone in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment and for 2 months after the last dose. Due to enzyme induction, primidone (and main metabolitephenobarbital) may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods (see sections 4.5 and 4.6).

Women planning a pregnancy should be advised to consult in advance with her physician so that adequate counselling can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with primidone.

Precautions for use

Primidone, like phenobarbital, is an enzyme inducer and can thus potentially reduce the efficacy of certain medicinal products due to a progressive increase in their metabolism (see section 4.5).

Concomitant intake of this medicinal product with alcoholic beverages or with medicinal products containing alcohol is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its enzyme inducer properties, primidone may increase metabolism of medicinal products, mainly those whose metabolism involves iso-enzymes of cytochrome P450 3A.

Contraindications of concomitant use

ANTIVIRALS	
Cobicistat	Risk of lack of efficacy due to increased metabolism induced by primidone
Daclatasvir, desabuvir, ledipasvir, nelfinavir, ombitasvir + paritaprevir, rilpivirine	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
Sofosbuvir	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Telaprevir	Risk of decreased plasma concentrations
ANTIFUNGALS	
Voriconazole, isavuconazole	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
DRUGS AFFECTING THE NERVOUS SYSTEM (except antiepileptics)	
Lurasidone	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
ANTI-INFECTIVES	
Delamanid	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
OTHER THERAPEUTIC CLASSES	
Cholic acid	Antagonist effect of primidone
St. John's wort	Risk of decreased primidone plasma concentrations and risk of lack of efficacy

Concomitant use not recommended

DRUGS AFFECTING THE NERVOUS SYSTEM (except antiepileptics)	
Mianserin	Risk of lack of efficacy of mianserin
Oxycodone	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
Quetiapine	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Sertraline	Risk of lack of efficacy due to increased metabolism induced by primidone

ANTI-INFECTIVES	
Telithromycin	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Bedaquiline	Risk of lack of efficacy due to increased metabolism induced by primidone
ANTINEOPLASTIC AGENTS	
Tyrosine kinase inhibitors	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Eribulin	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
Ifosfamide	Risk of increased neurotoxicity due to increased metabolism induced by primidone
ANTIVIRALS	
Boceprevir	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Clinical and laboratory parameters monitoring, especially at initiation of combination.
Simeprevir	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
ANTIFUNGALS	
Itraconazole	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
ANTICOAGULANTS	
Apixaban, dabigatran, rivaroxaban, ticagrelor	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
CARDIOVASCULAR DRUGS	
Bosentan	Risk of decreased plasma concentrations
Nimodipine, dronedarone, macitentan	Risk of decreased plasma concentrations due to increased metabolism induced by primidone
Ranolazine	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
HORMONAL AGENTS	
Abiraterone, Ulipristal	Risk of lack of efficacy due to increased metabolism induced by primidone
Estro-progestative combination contraceptive	Risk of lack of efficacy due to increased metabolism induced by primidone Preferably use another contraceptive method during combination and the following cycles (see section 4.6)
OTHER THERAPEUTIC CLASSES	
Alcohol	Increased risk of sedative effects of primidone and alcohol
Ivacaftor, praziquantel	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone

Other interactions

OTHER ANTIEPILEPTICS	
Carbamazepine	Progressive decrease of plasma levels of carbamazepine and its active metabolite, without apparent changes in antiepileptic effect Precautions requiring a careful interpretation of plasma concentrations
Felbamate	Risk of decreased plasma concentrations and risk of lack of efficacy of felbamate due to increased metabolism induced by primidone Risk of increased plasma concentrations of primidone Precautions requiring clinical and laboratory parameter monitoring and dose adjustment of primidone.
Lamotrigine	Risk of decreased plasma levels and increased metabolite plasma levels due to increased metabolism induced by primidone

	Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination and after primidone discontinuation
Oxcarbazepine	1. Risk of decreased plasma levels of primidone (due to increased metabolism induced by oxcarbazepine). 2. Risk of decreased plasma levels of oxcarbazepine (due to increased metabolism induced by primidone).Precautions requiring clinical and laboratory parameter monitoring and dose adjustment of oxcarbazepine/primidone
Perampanel	Risk of decreased plasma concentrations of perampanel Precautions
Phenytoin	1. In the event of previous treatment with primidone and addition of phenytoin: risk of increased plasma levels of primidone and risk of overdose (due to decreased metabolism induced by phenytoin). 2. In the event of previous treatment with phenytoin and addition of primidone, unpredictable interactions: 1. Decreased plasma levels of phenytoin (due to increased metabolism induced by primidone). Risk of overdose with phenytoin in case of primidone discontinuation. 2. Risk of increased plasma levels of phenytoin (due to decreased metabolism).Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination and after primidone/phenytoin discontinuation
Stiripentol	Risk of increased plasma levels of primidone due to decreased metabolism induced by stiripentol Precautions requiring clinical and laboratory parameter monitoring and dose adjustment of primidone.
Tiagabine	Risk of decreased plasma levels due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment of tiagabine
Valproic acid	1. Risk of increased plasma levels of primidone and risk of overdose of primidone (due to decreased metabolism induced by valproic acid). 2. Risk of decreased plasma levels of valproic acid (due to increased metabolism induced by primidone). 3. Risk of hyperammonaemia, with increased risk of encephalopathy

	Precautions requiring clinical and laboratory parameter monitoring and dose adjustment of primidone/valproic acid
Zonisamide	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
DRUGS AFFECTING THE NERVOUS SYSTEM (except antiepileptics)	
Benzodiazepines	Increased risk of nervous system depression and increased risk of respiratory depression which may be fatal in case of overdose
Methadone	Risk of lack of efficacy and withdrawal syndrome due to increased metabolism induced by primidone Precautions requiring monitoring and dose adjustment during combination after primidone discontinuation
Morphine-like agents (including fentanyl)	Increased risk of respiratory depression which may be fatal in case of overdose. Risk of decreased plasma concentrations due to increased metabolism induced by primidone.
ANTIINFECTIVES	
Doxycycline	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination
Metronidazole	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
Quinine	Risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
ANTINEOPLASTIC AGENTS	
Cabazitaxel, docetaxel	Risk of lack of efficacy due to increased metabolism induced by primidone
Irinotecan	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Procarbazine	Risk of increased hypersensitivity reactions (hypereosinophilia, rash) due to increased metabolism induced by primidone
ANTIVIRALS	
Dolutegravir	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring monitoring and dose adjustment during combination after primidone discontinuation
Maraviroc	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination after primidone discontinuation
Protease inhibitors in combination with ritonavir (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir)	Risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring clinical and laboratory

	parameter monitoring especially at treatment initiation
ANTIFUNGALS	
Albendazole, posaconazole	Risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
ANTICOAGULANTS	
Vitamin K antagonists (acenocoumarol, fluindione, phenindione, warfarin)	Risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring INR monitoring and dose adjustment during combination and 8 days after primidone discontinuation
CARDIOVASCULAR DRUGS	
Calcium channel blockers	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination and after primidone discontinuation.
Beta-blockers (metoprolol, propranolol)	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Class IA antiarrhythmics	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring monitoring (clinical, ECG, laboratory parameters) and dose adjustment during combination and after primidone discontinuation
Ivabradine	Risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
Propafenone	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring clinical monitoring (ECG) and dose adjustment during combination and after primidone discontinuation
HORMONAL AGENTS	
Androgens	Risk of decreased androgen plasma concentrations and risk of lack of efficacy, due to increased metabolism induced by primidone Precautions requiring clinical and laboratory parameter monitoring during combination and 1-2 weeks after primidone discontinuation
Glucocorticoids and mineralocorticoids	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination after primidone discontinuation
Thyroid hormones	Risk of lack of efficacy due to increased metabolism of T3 and T4 induced by primidone Precautions requiring laboratory parameter monitoring (T3 and T4 plasma levels) and dose adjustment during combination after primidone discontinuation
Non-contraceptive estro-progestative combination	Risk of lack of efficacy due to increased metabolism

	induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation
OTHER THERAPEUTIC CLASSES	
Beta-2 antagonists (metoprolol, propranolol)	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone
Folates	Risk of decreased plasma concentrations of primidone due to its increased metabolism (in which folates are a cofactor) Precautions requiring clinical and laboratory parameter monitoring and dose adjustment during combination after folates discontinuation
Immunosuppressant agents (ciclosporin, tacrolimus, sirolimus, everolimus)	Risk of decreased plasma concentrations and risk of lack of efficacy due to increased metabolism induced by primidone Precautions requiring laboratory parameter monitoring and dose adjustment during combination and after primidone discontinuation
Iron chelators (deferasirox)	Risk of decreased plasma concentrations due to increased metabolism induced by primidone Precautions requiring monitoring of iron blood levels and dose adjustment during combination after primidone discontinuation
Montelukast, theophylline	Risk of decreased plasma concentrations and risk of lack of efficacy, due to increased metabolism induced by primidone Precautions requiring clinical monitoring and dose adjustment during combination and after primidone discontinuation

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Primidone is extensively metabolised to phenobarbital. Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with primidone in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment with primidone and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods while on treatment with primidone, e.g. two complementary forms of contraception including a barrier method, oral contraceptive containing higher doses of oestrogen, or a non-hormonal intrauterine device (see section 4.5).

Women of childbearing potential should be informed of and understand the risk of potential harm to the foetus associated with phenobarbital use during pregnancy and the importance of planning a pregnancy.

Women planning a pregnancy should be advised to consult in advance with her physician so that specialist medical advice can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with primidone.

Pregnancy

Risks related to epilepsy and to antiepileptic drugs:

Specialist medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risks related to primidone and its main metabolite phenobarbital:

Studies in animals have demonstrated reproductive toxicity, including teratogenicity and effects on memory and learning (see section 5.3). Primidone is extensively metabolised to phenobarbital. Phenobarbital crosses the placenta. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Data from meta-analysis and observational studies showed a risk of major malformations about 2 to 3 times higher than the baseline risk of major malformations in the general population (which is 2-3%). The risk is dose-dependent; however, no dose has been found to be without risk. Phenobarbital monotherapy is associated with an increased risk of major congenital malformations, including cleft lip and palate and cardiovascular malformations. Other malformations involving various body systems including cases of hypospadias, facial dysmorphic features, neural tube effects, craniofacial dysmorphia (microcephaly) and digital abnormalities have also been reported.

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length, compared to lamotrigine monotherapy.

Neurodevelopmental disorders have been reported among children exposed to phenobarbital during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenobarbital during pregnancy are contradictory and a risk cannot be excluded. Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Primidone should not be used during pregnancy unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.

If, following re-evaluation of treatment with primidone, no other treatment option is suitable, the lowest effective dose of primidone should be used. The woman should be fully informed of and understand the risks related to the use of primidone during pregnancy.

When used in the third trimester of pregnancy, withdrawal symptoms may occur in the neonate, including sedation, hypotonia and sucking disorder.

Patients taking primidone should be adequately supplemented with folic acid before conception and during pregnancy.

Neonates
Antiepileptic drugs, particularly phenobarbital, a metabolite of primidone, can induce:

- Sometimes, a bleeding syndrome within the first 24 hours of life in a treated mother's newborn. 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.
- Symptoms related to the neonate's absorption of phenobarbital, particularly sedation, hypotonia and poor suckling;
- Rarely: withdrawal syndrome (abnormal movements, inefficient suckling).

Breast-feeding

Since primidone is excreted into breast milk and it may induce sedative effects. Unless there is an absolute need for the baby, breast-feeding is not recommended during maternal primidone therapy and if breast-fed, the baby should be monitored for sedation.

Fertility

No human data are available on the effect of primidone on fertility. In animals, effects on fertility have been observed (see section 5.3)

4.7 Effects on ability to drive and use machines

Due to the risk of somnolence, visual disturbances and impaired reaction time, primidone has a major impact on the ability to drive and use machines.

4.8 Undesirable effects

At treatment initiation, the most common adverse reactions are somnolence, dizziness and ataxia; these may disappear with treatment continuation and/or dose reduction.

Occasionally an idiosyncratic reaction may occur involving visual disturbances, nausea, headache, dizziness, vomiting, nystagmus and ataxia; these symptoms are usually transient even when marked. When these reactions are acute and severe, treatment withdrawal is required.

Other adverse reactions, observed during post-marketing surveillance, may include:
Frequencies are defined as: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Tabulated list of adverse events

Frequency	**System Organ Class**	**Adverse reactions**
Common (>1/100, <1/10)	Nervous system disorders	Ataxia, nystagmus
	Gastrointestinal disorders	Nausea
	Psychiatric disorders	Apathy
Uncommon (>1/1,000, <1/100)	Nervous system disorders	Headache, dizziness
	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders	Allergic reactions particularly affecting the skin, which can include: rash maculo-papular, rash morbilliform or rash scarlatiniform.
Rare (>1/10,000, < 1/1,000)	Blood and lymphatic system disorders	Anaemia megaloblastic*, leukopenia, thrombocytopenia, lymphadenopathy
	Psychiatric disorders	Psychotic disorder, libido disorder
	Nervous system disorders	Somnolence
	Musculoskeletal and connective tissue disorders	Arthralgia, osteomalacia**. As with phenobarbital, Dupuytren's contracture
	Skin and subcutaneous tissue disorders	Dermatitis exfoliative, systemic lupus erythematosus.
	Investigations	Hepatic enzymes increased, including gamma-glutamyl transferase (gamma GT) and

		blood alkaline phosphatase
Very rare (<1/10,000)	Skin and subcutaneous tissue disorders	Severe skin reaction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4)
Unknown	Metabolism and nutrition disorders	Decreased appetite
	Psychiatric disorders	Suicidal ideation***, confusional state, hallucination
	Nervous system disorders	Balance disorder
	Skin and subcutaneous tissue disorders	Hypersensitivity syndrome: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), pruritus.
	Investigations	Bone density decreased
	Musculoskeletal and connective tissue disorders	Osteopenia, osteoporosis and fracture in patients receiving long-term therapy****
	General disorders and administration site conditions	Fatigue
	Eye disorders	Visual impairment

* Exceptionally, as is the case with phenytoin and phenobarbital, primidone can cause megaloblastic anaemia requiring discontinuation of the drug. 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.
******* see section 4.4 Special warnings and precautions for use
****The mechanism that affects bone metabolism has not been identified.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Primidone is metabolised into phenobarbital, with a highly variable rate depending on the patient. Overdose may cause varying degrees of CNS depression which, depending on the dose ingested, may include ataxia, loss of consciousness, respiratory depression and coma.

Crystalluria may occur with overdose. This could be a useful diagnostic aid when primidone overdose is suspected.

Depending on the severity of poisoning, for therapy the stomach should be emptied, administration of activated charcoal, intravenous administration of fluids, forced alkaline diuresis (to obtain a urine pH of 8.0), and other general support measures should be instituted as required. 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).
ATC code: N03AA03

Mysoline's action is due to the anticonvulsant properties of three active moieties, namely primidone itself and its two main metabolites, phenobarbital and phenylethylmalonamide (PEMA). The relative contribution of these three moieties to the clinical anticonvulsant effect has not been firmly established.

Although Mysoline's precise mechanism of action is unknown, like other anticonvulsants, such as barbiturates and derivatives, these compounds are known to directly modulate neuronal membrane excitability through:

- Prolongation and potentiation of the effect of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS: barbiturates act as positive allosteric modulators, and at higher doses as agonists of $GABA_A$ receptors.
- Inhibition of the effect of glutamate, the principal excitatory neurotransmitter in the CNS: barbiturates block AMPA and kainate receptors, subtypes of glutamate receptors.

The combination of these various actions likely accounts for their anticonvulsant activity, but also probably for their associated adverse reactions.

5.2 Pharmacokinetic properties

Absorption
Primidone is absorbed rapidly from the gastrointestinal tract. Peak plasma levels are reached approximately 3 hours after ingestion.

Distribution
Primidone is well distributed in all organs and tissues. It crosses the blood-brain and placental barriers and is excreted in breast milk (see section 4.6). Primidone is only partially bound to plasma proteins (by about 35%) because of its physical-chemical properties.

Biotransformation
Primidone is partially metabolised in the liver into two metabolites, phenobarbital and phenylethylmalonamide (PEMA), that have anticonvulsant activity.

Elimination
Primidone has an elimination half-life of approximately 10 hours, which is considerably shorter than that of its principal metabolites (16 hours for PEMA and 70 hours for phenobarbital). Approximately 40% of the drug is excreted unchanged in urine, mainly in the form of primidone or PEMA.

5.3 Preclinical safety data

Repeated dose toxicity
Centrilobular hepatocyte hypertrophy and chronic nephropathy have been observed in rats administered clinically relevant doses of primidone for 14 weeks. Hepatocellular hypertrophy has also been observed in dogs administered clinically relevant doses of primidone for 6-months.

Genotoxicity
Primidone was shown to be mutagenic in one strain of *Salmonella typhimurium* (TA1535). Other *in vitro* and *in vivo* tests did not demonstrate genotoxicity. Therefore, the risk of genotoxicity to humans is unknown.

Carcinogenicity
Standard 2-year carcinogenicity studies have identified an increased incidence of hepatocellular neoplasms in male and female mice, thyroid adenomas in male mice and male rats, and combined incidences of renal tubule adenomas or carcinomas in male rats at doses considered clinically relevant. The risk of carcinogenicity to humans is unknown.

Reproductive toxicity
Animal studies have shown that primidone is teratogenic and impairs post-natal development at doses considered to be clinically relevant. Teratogenic effects in mice included palate defects, enlargement of cerebral ventricles, club foot, open eyes and haemorrhages within the subarachnoid space. Primidone was also shown to be embryolethal in mice and rats at clinically relevant doses. Effects on post-natal development include impairment of memory and learning development in male rats from litters of dosed female rats. Effects on fertility in animals have been observed at doses considered to be clinically relevant. Primidone induced a reduction in seminal vesicle weight and an increase in oestrous cycle length in mice. In a 5-day study in male mice, primidone induced a dose-dependent increase in sperm-head abnormalities.

Published studies reported teratogenic effects (morphological defects) in rodents exposed to phenobarbital (main metabolite of primidone). Cleft palate is reported consistently in all preclinical studies but other malformations are also reported (e.g. umbilical hernia, spina bifida, exencephaly, exomphalos plus fused ribs) in single studies or species.

In addition, although data from the published studies are inconsistent, phenobarbital given to rats/mice during gestation or early postnatal period was associated with adverse neurodevelopment effects, including alterations in locomotor activity, cognition and learning patterns.

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.
Store in the original outer carton.
Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottle (100 tablets).
Box of 10 PVC/aluminum blisters, each containing 10 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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40 avenue George V
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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT