# NEW ZEALAND DATA SHEET

## 1. PRIMIDONE (250mg tablets)

PRIMIDONE 250mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Primidone 250mg

***Excipient(s) with known effect***

None

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

PRIMIDONE 250mg tablets are white, round (diameter of 10.4mm), flat with bevelled edge tablets, scored and engraved -with 250 on one side. The other side is plain. Each tablet contains 250mg primidone and typically weighs 340mg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- 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 Dose and method of administration

***Dose***

Treatment must always be individualised. In many patients it will be possible to use PRIMIDONE alone but in some it will need to be combined with other anti-convulsants.

PRIMIDONE is usually given twice daily. Start with 125mg once daily late in the evening. Every three days increase the daily dose by 125mg until the patient is receiving 500mg daily. Thereafter, every three days increase the daily dose by 250mg in adults or 125mg in children under 9 years of age until control is obtained or the maximum tolerated dosage is being given. This may be as much as 1,500mg per day in adults and 1,000mg per day in children.

***Average daily maintenance doses:***

Children up to 2 years: 250mg to 500mg per day

Children 2 to 5 years: 500mg to 750mg per day

Children 6 to 9 years: 750mg to 1,000mg per day

Adults and children over 9 years: 750mg to 1,500mg per day.

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

seizures are more frequent e.g. if the attacks are nocturnal then all or most of the day's dose may be given at night; if the attacks are associated with some particular event such as menstruation a slight increase at the appropriate time is often beneficial.

### *Patients on other anti-convulsants*

Where a patient's attacks are not sufficiently well controlled with other anti-convulsants, or disturbing side effects have arisen, PRIMIDONE may be used to augment or replace existing treatment.

First add PRIMIDONE to the current anti-convulsant treatment by the gradual introduction described previously. When a worthwhile effect has been achieved and the amount of PRIMIDONE being given has been built up to at least half the estimated requirement withdrawal of the previous treatment can then be attempted. This should be done gradually over a period of two weeks during which time it may be necessary to increase the PRIMIDONE 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 PRIMIDONE substitution should be made earlier to prevent excessive drowsiness from interfering with accurate assessment of the optimum dosage of PRIMIDONE.

### *Paediatric population*

Please refer to dose section above

### *Method of administration*

Tablets are to be taken orally with a glass of water

### *Maximum Tolerated Daily Dose*

2000mg

## 4.3 Contraindications

- Hypersensitivity or allergic reactions to primidone.
- Acute intermittent porphyria.

## 4.4 Special warnings and precautions for use

Primidone should be given with caution and may be required in reduced dosage in patients with impaired respiratory function.

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

### *Women of childbearing potential*

Primidone is extensively metabolised to phenobarbital. As a consequence, Primidone may cause fetal harm when administered to a pregnant woman. Prenatal exposure to primidone may increase the risk for congenital malformations and adverse developmental outcomes (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, women planning pregnancy, and pregnant women should be fully informed of the potential risk to the fetus if they take primidone during pregnancy.

### *Vitamin D*

Primidone may affect Vitamin D metabolism, which may predispose to the development of bone disease. There are reports that long term use may lead to a reduction of bone mineral density and therefore development of osteoporosis (Petty, S.J. et al, Neurology, 65: 1358-1363, 2005). Patients on long term treatment should be monitored for bone density and supplementation with Vitamin D should be considered.

### *Aggravated convulsions*

As with other antiepileptic drugs, some patients may experience, instead of an improvement, a worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with primidone. For patients on primidone, cases of these aggravations may be indicative of an inadequate choice of treatment for the epileptic syndrome, a result of a change of the concomitant anti-epileptic treatment or a pharmacokinetic interaction, a toxicity or overdose.

### *Treatment cessation*

Sudden withdrawal of a treatment at efficient anti-epileptic doses may induce convulsive fits and epilepticus status, mainly in cases of alcoholism.

Primidone is a potent central nervous system (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.

### *Suicidal behaviour and ideation*

Antiepileptic drugs (AEDs), including primidone, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any Antiepileptic drugs AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/ or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5- 100 years) in the clinical trials analysed. **Table *1***shows absolute and relative risk by indication for all evaluated AEDs.

**Table 1 Risk by indication for antiepileptic drugs in the pooled analysis**

| Indication | Placebo patients with events/1000 patients | Drug patients with events/1000 patients | Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients | Risk Difference: Additional Drug patients with events per 1000 patients |
|---|---|---|---|---|
| Epilepsy | 1.0 | 3.4 | 3.5 | 2.4 |
| Psychiatry | 5.7 | 8.5 | 1.5 | 2.9 |
| Other | 1.0 | 1.8 | 1.9 | 0.9 |
| Total | 2.4 | 4.3 | 1.8 | 1.9 |

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing primidone or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

### *Severe skin reactions*

Life threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) 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 or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters of mucosal lesions) are present, primidone treatment should be discontinued.

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

### *Use in hepatic impairment*

Primidone should be given with caution and may be required in reduced dosage in patients with impaired hepatic function.

### *Use in renal impairment*

Primidone should be given with caution and may be required in reduced dosage in patients with impaired renal function.

### *Use in the elderly*

Primidone should be given with caution and may be required in reduced dosage in the elderly.

### *Use in debilitated patients*

Primidone should be given with caution and may be required in reduced dosage in debilitated patients.

### *Paediatric use*

Primidone should be given with caution and may be required in reduced dosage in children.

### *Effects on laboratory tests*

No data available

## 4.5 Interaction with other medicines and other forms of interaction

Both primidone and its major metabolite, phenobarbitone, induce liver enzyme activity; both primidone and phenobarbitone are strong inducers of cytochrome P450. This may lead to altered pharmacokinetics in concomitantly administered drugs including other anticonvulsant drugs, e.g. phenytoin and coumarin anticoagulants. Such interactions may lead to life-threatening situations due to the risk of decreased plasma concentrations and consequently, lack of efficacy of co-administered medications.
Blood levels of both primidone and any additional anticonvulsant agent may be altered by concomitant administration.

### *Concomitant use not recommended*

• Risk of decreased plasma concentrations due to increased metabolism induced by primidone for:
- Drugs affecting nervous system* (except anti-epileptics): lurasidone, mianserin, oxycodone, quetiapine, sertraline.
- Anti-infective agents: delamanide, telithromycine, bedaquiline.
- Anti-neoplastic agents: tyrosine kinase inhibitors, ifosfamide (+ risk of increased neurotoxicity of ifosfamide due to increased metabolism induced by primidone).
- Antivirals: cobicistat, daclatasvir, dasabuvir, ledipasvir, nelfinavir, rilpivirine, ombitasvir+paritaprevir, sofosbuvir, telaprevir, boceprevir, simeprevir.
- Antifungal agents: voriconazole, isavuconazole, itraconazole.
- Anticoagulant drugs: apixaban, dabigatran, rivaroxaban, ticagrelor.
- Cardiovascular agents: bosentan, nimodipine, dronedarone, macitentan, ranolazine.
- Hormonal agents: abiraterone, ulipristal.
- Other therapeutic classes: alcohol (+ increased risk of sedative effects of primidone and alcohol), ivacaftor, praziquantel.

• Risk of decreased primidone plasma concentrations and risk of lack of efficacy for:
- St John's wort.

### *Precaution – concomitant use may require dosage adjustment*

• Risk of decreased plasma concentrations due to increased metabolism induced by primidone for:
- Other anti-epileptics: carbamazepine; felbamate; lamotrigine; oxcarbazepine (+ risk of decreased plasma levels of primidone by increased metabolism induced by oxcarbazepine); perampanel; phenytoin (+ risk of increased phenobarbital concentrations and possible toxicity. Possible toxicity with phenytoin on stopping primidone); stiripentol, tiagabine, valproic acid, zonisamide.
- Drugs affecting nervous system* (except anti-epileptics): benzodiazepines, methadone, opioid agents (including fentanyl).
- Anti-infective agents: doxycycline, metronidazole, quinine (+ risk of increased phenobarbital concentrations and possible toxicity).
- Anti-neoplastic agents: carbazitaxel, docetaxel, irinotecan, procarbazine (+ risk of increased hypersensitivity reactions: hypereosinophilia, rash).
- Antivirals: dolutegravir; maraviroc; protease inhibitors in combination with ritonavir (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir): risk of decreased

primidone concentrations due to CYP3A4 significant inhibition properties of the combination protease inhibitors-ritonavir.
- Antifungal agents: albendazole, posaconazole.
- Anticoagulant drugs: antivitamin K drugs (acenocoumarol, phenindione, warfarin): INR monitoring required.
- Cardiovascular agents: calcium channel blockers; beta-blockers (metoprolol, propranolol); class I A antiarrhythmic, ivabradine, propafenone.
- Hormonal agents: androgens; glucocorticosteroids and mineralocorticosteroids; thyroid hormones.
- Other therapeutic classes: non-contraceptive estrogens; folates; immunosuppressant agents (cyclosporin, tacrolimus, sirolimus, everolimus); iron-chelators (deferasirox); theophylline.

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

*The effects of other CNS depressants (e.g. alcohol and barbiturates) may be enhanced by the administration of primidone.

## 4.6 Fertility, pregnancy and lactation

### *Women of childbearing potential*

Primidone 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.

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

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

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

Women should be advised to contact their doctor immediately if they become pregnant or think they may be pregnant and are taking primidone.

### *Contraception*

Women of childbearing potential should use effective contraception during treatment with primidone and for two months after stopping treatment. Due to enzyme induction, primidone may result in a failure of the therapeutic effect of oral contraceptive drugs (see section 4.5).

Women should be advised that at least one highly effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

### *Pregnancy*

Category D

Primidone is extensively metabolised to phenobarbital. Phenobarbital metabolites readily cross the placenta following oral administration and are distributed throughout fetal tissue.

It is, recommended that:

- Women on antiepileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of congenital malformations and adverse developmental outcomes;
- AEDs should be continued during pregnancy at the lowest effective dose and monotherapy should be used if appropriate;
- Adequate folic acid supplementation should be discussed as part of pre-pregnancy and pregnancy

counselling;

- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be considered.

Specialist medical advice regarding the potential risks to a fetus 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.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

Primidone therapy in pregnant women with epilepsy presents a risk to the fetus due to the major and minor congenital defects including congenital craniofacial and cardiac defects, digital abnormalities and, less commonly, cleft lip and palate associated with the phenobarbital metabolites produced from primidone.

Studies in women with epilepsy who were exposed to phenobarbital during pregnancy identified a frequency of major malformations of 6-7% in their offspring compared to the background rate in the general population of 2-3%. Studies have found the risk of congenital malformations following in-utero exposure to phenobarbital to be dose-dependent, however,no dose has been found to be without risk. Therefore, the lowest effective dose of primidone (and phenobarbital) should be used.

The use in pregnancy of primidone, phenobarbitone or methylphenobarbitone has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability.

### *In neonates*

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length to women with epilepsy who were exposed to phenobarbital during pregnancy compared to women exposed to lamotrigine monotherapy during pregnancy. As primidone is extensively metabolised to phenobarbital, this is a potential risk for infants exposed to primidone.

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K1 for the mother before delivery (as well as the neonate) is recommended and the neonate should be monitored for signs of bleeding.

### *Breast-feeding*

During breastfeeding the infant should be monitored for sedation.

### *Fertility*

No data available

## 4.7 Effects on ability to drive and use machines

Patients who drive or operate machinery should be aware of the possibility of impaired reaction time. Likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

## 4.8 Undesirable effects

If side effects do occur they are generally confined to the early stages of treatment, patients frequently feel drowsy and listless.

Visual disturbances, nausea, headache, dizziness, vomiting, nystagmus and ataxia have been reported, but these are usually transient even when pronounced. On occasions idiosyncratic reactions may occur which involves symptoms in an acute and severe form necessitating withdrawal of treatment. Dermatological reactions including severe skin eruptions and, rarely, systemic conditions (e.g. systemic lupus erythematosus) have been reported. Occasional cases of arthralgia and, rarely, personality

changes (which may include psychotic reactions) have been reported. As with phenobarbitone, in rare cases Dupuytren's contracture has been reported in patients administered primidone.

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 cyanocobalamin (vitamin B12). There have been isolated reports of other blood dyscrasias.

The following adverse events have been observed in patients taking primidone at an unknown frequency: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome, decreased bone density, osteopenia and fractures in patients on long term therapy, apathy, megaloblastic anaemia, leucopenia, thrombocytopenia, lymphadenopathy and exfoliative dermatitis. See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Severe skin reactions.**

Behaviour changes like suicidal behaviour, suicidal ideation and emergence or worsening of existing depression should be closely monitored.

**Table 2 Adverse Effects listed by System Organ Class**

| System Organ Class | Adverse Effects |
|---|---|
| Blood and lymphatic system disorders | Blood dyscrasia<br>Leucopenia<br>Thrombocytopenia<br>Lymphadenopathy |
| Metabolism and nutrition disorders | Megaloblastic anaemia |
| Psychiatric disorders | Listlessness<br>Personality Change<br>Psychosis<br>Suicidal behaviour<br>Suicidal ideation<br>Depression (emerging or worsening) |
| Nervous system disorders | Drowsiness<br>Dizziness<br>Headache<br>Ataxia<br>Nystagmus |
| Eye disorders | Visual disturbances |
| Gastrointestinal disorders | Nausea<br>Vomiting |
| Skin and subcutaneous tissue disorders | Rash<br>Systemic lupus erythematosus<br>Stevens-Johnson syndrome (SJS)<br>Toxic epidermal necrolysis (TEN)<br>Hypersensitivity syndrome<br>Exfoliative dermatitis |
| Musculoskeletal and connective tissue disorders | Arthralgia |

| | |
|---|---|
| | Dupuytren's contracture<br>Decreased bone density<br>Osteopenia<br>Factures |

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

### 4.9 Overdose

***Symptoms***

Primidone is metabolised extensively to phenobarbitone and overdosage leads to various degrees of CNS depression which depending on the dosage ingested may include ataxia, loss of consciousness, respiratory depression and coma.

***Treatment***

Treatment should include aspiration of stomach contents and general supportive measures. There is no specific antidote.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

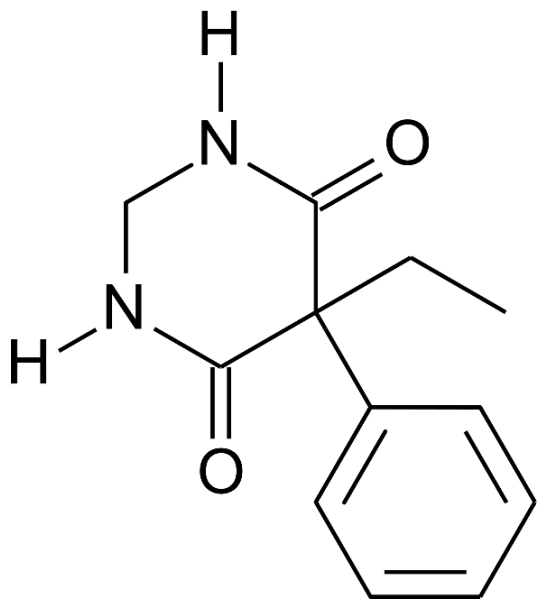
***Pharmacotherapeutic group:***

Antiepileptic

***ATC code:***

N03AA03

***Chemical Structure:***




***Mechanism of action***

Primidone is an anti-convulsant, anti-epileptic agent. The anti-convulsant properties of primidone are partly attributable to primidone itself and partly to its metabolites phenobarbitone and phenylethylmalonamide. The medicine reduces the sensitivity of the central nervous system to fit inducing stimuli but its precise mode of action is obscure although enhancement of release of inhibitory transmitters may occur.

***Pharmacodynamic effects***

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

Primidone may also affect vitamin D metabolism which may predispose to the development of bone disease.

## 5.2 Pharmacokinetic properties

***Absorption***

Primidone is readily absorbed from the gastro-intestinal tract and is reported to have a plasma half-life ranging from 10 to 15 hours which is shorter than those of the principal metabolites – phenobarbitone and phenylethylmalonamide both of which are active. The time to peak plasma levels can vary markedly.

***Distribution***

Primidone is widely distributed but is only partially bound to plasma protein – it has been suggested that it exhibits variable binding up to about 20%. Primidone and its metabolites readily cross the blood-brain barrier. Primidone also crosses the human placenta and is excreted in breast milk.

### *Biotransformation*

Metabolism to phenobarbitone is slow and not linearly related to dose. Conversion to phenylethylmalonamide is proportional to dose and this compound is cleared with an apparent half-life of 22 to 24 hours. The hydroxylated parent drug has also been identified as a minor metabolite.

### *Elimination*

The elimination half-life in epileptic patients (including children) and healthy volunteers is about 8 hours. This increases to about 14 hours in uraemic subjects but reduced to 5 hours during dialysis. Steady state levels are directly proportional to the daily dose.

In a group of epileptic children 92% of the administered dose could be accounted for by parent drug and metabolites in urine, indicating that renal excretion was the major route of elimination.

## 5.3 Preclinical safety data

### *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 palatal defects, enlargement of cerebral ventricles, club foot, open eyes and haemorrhages within the subarachnoid space. Primidone was also shown to be embryo lethal in mice and rats at clinically relevant doses. Post-natal development effects 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 estrous cycle length in mice. In a 5-day study in male mice, primidone induced a dose-dependent increase in sperm-head abnormalities.

### *Genotoxicity*

No data available

### *Carcinogenicity*

No data available

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

PRIMIDONE contains the following excipients:

- Methylcellulose
- Croscarmellose sodium
- Magnesium stearate
- Colloidal silicon dioxide

## 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

Shelf life: 5 years from the date of manufacture

### 6.4 Special precautions for storage

Store at or below 25°C

Protect from heat light and moisture.

### 6.5 Nature and contents of container

PRIMIDONE250mg: HDPE bottles containing 100 or 500 tablets Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

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

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

## 9. DATE OF FIRST APPROVAL

02 August 2012

## 10. DATE OF REVISION OF THE TEXT

29 June 2026

***Summary table of changes***

| Section changed | Summary of new information |
|---|---|
| 4.4 | Updated to include additional safety warnings and precautions, including risks in special populations, suicidal ideation, severe skin reactions, seizure aggravation and guidance on treatment discontinuation. |
| 4.5 | Expanded to include detailed information on clinically significant drug interactions, medicines not recommended for concomitant use and those requiring dose adjustment, including effects on hormonal contraception. |
| 4.6 | Added the text regarding use in pregnancy and in neonates. |
| 4.8 | Addition of adverse events. Alignment with Medsafe template |
| 4.9 | Editorial changes to align with Medsafe template |
| 5.3 | Addition of animal study data on reproductive toxicity |