# 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 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.

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving antiepileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for

suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

Exceptionally, as with phenytoin and phenobarbitone, megaloblastic anaemia may develop requiring discontinuation of primidone. This condition may respond to treatment with folic acid and/or vitamin B12. There have been isolated reports of other blood dyscrasias.

## 4.5 Interaction with other medicines 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, clozapine, chloramphenicol, corticosteroids/glucocorticosteroids, cyclophosphamide, dicoumarins, digitoxin*, doxycycline, ethosuximide, etoposide, felbamate, granisetron, lamotrigine, losartan, methadone*, metronidazole, mianserin, montelukast*, nelfinavir*, nimodipine, oral-contraceptives, oxcarbazepine, phenytoin, quinidine, rocuronium, sodium valproate, tiagabine, theophyllines, topiramate, tricyclic antidepressants, vecuronium, warfarin and zonisamide.

Primidone inhibits the glucuronidation 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 Fertility, pregnancy and lactation

### *Pregnancy*

Category D

The risk of having an affected child as a result of medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

The risk of a mother with epilepsy and taking anti-convulsants giving birth to a baby with an abnormality is about three times that of the general population. Mothers taking more than one anti-convulsant

therapy have a higher risk of having a baby with a malformation than mothers taking one treatment. Women with epilepsy should take folic acid supplements of 5mg daily before and for 12 weeks after conception.

Withdrawal symptoms may occur in the newborn infant whose mother has received primidone in late pregnancy.

Long-term anti-convulsant 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 should be considered.

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.

The use in pregnancy of primidone either alone or in combination with other anti-convulsants can cause coagulation defects in the newborn infant which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery. 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, vitamin K1 10mg may be given to the mother at the time of delivery and 1mg should be given immediately to the neonate.

### *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.

On occasions idiosyncratic reactions may occur which involves symptoms in an acute and severe form necessitating withdrawal of treatment.

Exceptionally 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.

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

**Table 1 Adverse Effects listed by System Organ Class**

| System Organ Class | Adverse Effects |
|---|---|
| Blood and lymphatic system disorders | Blood dyscrasia |
| 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>Dizziness<br>Ataxia<br>Nystagmus |
| Eye disorders | Visual disturbances |
| Gastrointestinal disorders | Nausea<br>Vomiting |
| Skin and subcutaneous tissue disorders | Rash<br>Systemic lupus erythematosus |
| Musculoskeletal and connective tissue disorders | Arthralgia<br>Dupuytren's contracture |

***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://nzphvc.otago.ac.nz/reporting/}

## 4.9 Overdose

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

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic Properties

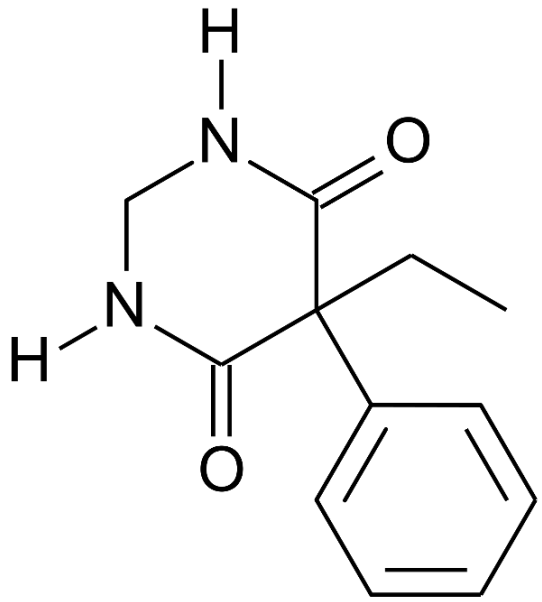
***Pharmacotherapeutic group:***

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

No information 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

27 October 2021

***Summary table of changes***

| Section changed | Summary of new information |
|---|---|
| 3 | Change to engraving on tablets. |