



## New Zealand Data Sheet

### APO-PRIMIDONE

#### Primidone 250mg Tablets

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#### **Presentation**

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

#### **Uses**

##### **Actions**

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.

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.

##### **Pharmacokinetics**

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.

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.

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.

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.

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.

##### **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.

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### Dosage and Administration

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

APO-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, APO-PRIMIDONE may be used to augment or replace existing treatment.

First add APO-PRIMIDONE to the current anti-convulsant treatment by the gradual introduction described previously. When a worthwhile effect has been achieved and the amount of APO-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 APO-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 APO-PRIMIDONE substitution should be made earlier to prevent excessive drowsiness from interfering with accurate assessment of the optimum dosage of APO-PRIMIDONE.

### Contraindications

Hypersensitivity or allergic reactions to primidone.

Acute intermittent porphyria.

### Warnings and Precautions

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 reactions on abrupt cessation of treatment.

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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 behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior 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 behavior that could indicate the emergence or worsening of suicidal thoughts or behavior 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.

### Use in Pregnancy and Lactation

Category D.

The risk of having an abnormal 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 B<sub>12</sub> should be considered.

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

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 K<sub>1</sub> through the last month of pregnancy up to the time of delivery. In the absence of such pretreatment, vitamin K<sub>1</sub> 10mg may be given to the mother at the time of delivery and 1mg should be given immediately to the neonate.

### Use during Lactation

During breastfeeding the infant should be monitored for sedation.

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### **Effect on ability to Drive or Operate Machinery**

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

### **Adverse Effects**

If side effects do occur they are generally confined to the early stages of treatment when 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 an idiosyncratic reactions may occur which involves these symptoms in an acute and severe form necessitating withdrawal of treatment.

Dermatological reactions including severe skin eruptions and rarely systemic conditions such as systemic lupus erythematosus have been reported. Occasional cases of arthralgia and rarely personality changes which may include psychotic reactions have been reported. In rare cases Dupuytren's contracture has been reported in patients administered primidone.

Exceptionally megaloblastic anaemia may develop requiring discontinuation of primidone. This condition may respond to treatment with folic acid and/or vitamin B<sub>12</sub>. There have been isolated reports of other blood dyscrasias.

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

### **Interactions**

Both primidone and its major metabolite phenobarbitone induce liver enzyme activity. This may lead to altered pharmacokinetics in concomitantly administered medicines including other anti-convulsants e.g. phenytoin and coumarin anti-coagulants.

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

The effect of other CNS depressants e.g. alcohol and barbiturates may be enhanced by the administration of primidone.

### **Overdosage**

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.

### **Pharmaceutical Precautions**

Store below 25°C.

### **Medicine Classification**

Prescription Only Medicine



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### Package Quantities

Bottle packs of 100 and 500 tablets.

### Further Information

Nil

### Name and Address

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