For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

Torvate

[Controlled Release Tablets of Sodium Valproate] (200 mg / 300 mg / 500 mg)

COMPOSITION

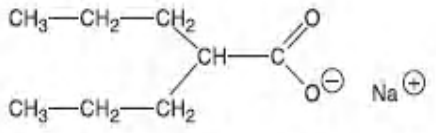
TORVATE 200
Each controlled release tablet contains :
Sodium Valproate I.P. 200 mg

TORVATE 300
Each controlled release tablet contains :
Sodium Valproate I.P. 300 mg

TORVATE 500
Each controlled release tablet contains :
Sodium Valproate I.P. 500 mg

DESCRIPTION

Sodium valproate is the sodium salt of valproic acid designated as sodium 2-propylpentanoate.
Its molecular formula is $C_8H_{15}O_2Na$ and the molecular weight is 166. It has the following structure:



CLINICAL PHARMACOLOGY

Pharmacodynamics
The most likely mode of action for Valproate is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).
Pharmacokinetic
The half-life of Valproate sodium is usually reported to be within the range 8-20 hours. It is usually shorter in children. In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels. The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological (or therapeutic) effects of Valproate sodium may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

INDICATIONS

Sodium valproate is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occurs either in isolation or in association with other type of seizures. It is also indicated for use as sole and adjunctive therapy in the

treatment of simple and complex absence seizures and adjunctive therapy in patients with multiple seizure types that includes absence seizures.

CONTRAINDICATION
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria
- Pregnancy
- Known urea cycle disorder

DOSAGES AND ADMINISTRATION
Daily dosage requirements vary according to age and body weight. Torvate tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed. In patients where adequate control has been achieved, formulations can be interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.
Dosage **Usual requirements are as follows:**
Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.
Children over 20kg
Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.
Children under 20kg
20mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.
Use in the elderly
Although the pharmacokinetics of Valproate sodium are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.
In patients with renal insufficiency
It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.
In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Valproate sodium since they employ the same metabolic pathway. Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid. Salicylates should not be used in children under 16 years. In addition in conjunction with Valproate sodium, concomitant use in children under 3 years can increase the risk of liver toxicity.
Combined Therapy
When starting Valproate sodium in patients already on other anticonvulsants, these should be tapered slowly: initiation of Valproate sodium therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose

by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Valproate sodium. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.
NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Women of childbearing potential should not be started on Valproate sodium without specialist neurological advice. Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus. Women who are taking Valproate sodium and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks. Valproate sodium is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Valproate sodium should be used only in patients resistant to other treatment. If pregnancy is planned, consideration should be given to cessation of Valproate sodium treatment, if appropriate. When Valproate sodium treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed.

Pregnancy

- Risk associated with epilepsy and antiepileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations. No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with seizures

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.

- Risk associated with valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.
In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium

valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy. Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy.
Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data

When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Valproate sodium during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Valproate sodium is prescribed for the first time or a woman already treated with Valproate sodium is planning a pregnancy. Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels. During pregnancy, Valproate sodium anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk. Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate.

- Risk in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Valproate sodium during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation

Excretion of Valproate sodium in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Valproate sodium, specifically haematological disorders

WARNINGS AND PRECAUTIONS

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.
There is variability in the plasma concentration when switching from one valproate brand to another brand, hence caution should be advised.

Special warnings

Liver dysfunction:

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age. The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years. Monotherapy is recommended in children under the age of 3 years when prescribing Valproate sodium, but the potential benefit of Valproate sodium should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk: non specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

In patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Valproate sodium therapy. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway. As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient. More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Valproate sodium should be discontinued.

Women of childbearing potential: A decision to use Valproate sodium in women of childbearing potential should not be taken without specialist neurological advice, and only if

the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Valproate sodium is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy.

Suicidal ideation and behaviour: Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Precautions

Haematological

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

Renal insufficiency

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Systemic lupus erythematosus

Although immune disorders have only rarely been noted during the use of Valproate sodium, the potential benefit of Valproate sodium should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Valproate sodium.

Weight gain

Valproate sodium very commonly causes weight gain, which may be marked and progressive.

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it.

Pregnancy

Women of childbearing potential should not be started on Valproate sodium without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus.

Diabetic patients

Valproate sodium is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Interaction with other medicinal products and other forms of interaction

Effects of Valproate sodium on other drugs

- Antipsychoticss, MAO inhibitors, antidepressants and benzodiazepines

Valproate sodium may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium

therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- Phenobarbital

Valproate sodium increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- Primidone

Valproate sodium increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Phenytoin

Valproate sodium decreases phenytoin total plasma concentration. Moreover Valproate sodium increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

- Carbamazepine

Clinical toxicity has been reported when Valproate sodium was administered with carbamazepine as Valproate sodium may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine

The risk of rash associated with the use of Valproate sodium may be increased if lamotrigine is also administered. Valproate sodium may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- Zidovudine

Valproate sodium may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- Vitamin K-dependent anticoagulants

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- Temozolomide

Co-administration of temozolomide and Valproate sodium may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Valproate sodium

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy. On the other hand, combination of felbamate and Valproate sodium may increase valproic acid plasma concentration. Valproate sodium dosage should be monitored. Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy.

Accordingly, the dosage of Valproate sodium may need adjustment.In case of concomitant use of Valproate sodium and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased. Valproic acid plasma levels may be increased (as a result of

reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin. Carbapenem antibiotics such as imipenem, panipenem and meropenem: Decrease in valproic acid blood level, sometimes associated with convulsions, has been reported when imipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproic acid blood levels is recommended. Colestyramine may decrease the absorption of Valproate sodium. Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

Other Interactions

Caution is advised when using Valproate sodium in combination with newer anti-epileptics whose pharmacodynamics may not be well established. Concomitant administration of valproate and topiramate has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy. Valproate sodium usually has no enzyme-inducing effect; as a consequence, Valproate sodium does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

ADVERSE EVENTS

Congenital and familial/genetic disorders:

Hepato-biliary disorders: Rare cases of liver dysfunction, severe liver damage, including hepatic failure sometimes resulting in death, have been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient.

Gastrointestinal disorders: (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Valproate sodium with or after food or by using Enteric Coated Valproate sodium. Very rare cases of pancreatitis, sometimes lethal, have been reported.

Nervous system disorders:

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported.

Encephalopathy and coma have very rarely been reported. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported. An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Metabolic disorders:

Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness.

Should these symptoms occur Valproate sodium should be discontinued. Very rare cases of hyponatraemia have been reported. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.

Blood and lymphatic system disorders:
Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia.
The blood picture returned to normal when the drug was discontinued. Bone marrow failure, including red cell aplasia. Agranulocytosis. Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Valproate sodium has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.
Skin and subcutaneous tissue disorders:
Rash rarely occurs with Valproate sodium. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.Transient hair loss, which may sometimes be dose-related, has often been reported. Re-growth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.
Reproductive system and breast disorders:
Amenorrhoea and irregular periods have been reported. Very rarely gynaecomastia has occurred.
Vascular disorders: The occurrence of vasculitis has occasionally been reported.
Ear disorders:
Hearing loss, either reversible or irreversible has been reported rarely; however a cause and effect relationship has not been established.
Renal and urinary disorders:
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.
Immune system disorders:
Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome, and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.
General disorders:
Very rare cases of non-severe peripheral oedema have been reported. Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored.

OVERDOSAGE
Cases of accidental and deliberate Valproate sodium overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.Signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose. Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported. Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion. Haemodialysis and haemoperfusion have been used successfully. Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

EXPIRY DATE
Do not use after the date of expiry

STORAGE
Keep in a dry place at a temperature not exceeding 30oC.

Marketed by:
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