

APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

EPILIM® LIQUID SUGAR-FREE (Liquid)

EPILIM® CR 200 (Prolonged release tablets)

EPILIM® CR 300 (Prolonged release tablets)

EPILIM® CR 500 (Prolonged release tablets)

EPILIM® 100 CRUSHABLE (Tablets)

EPILIM® INTRAVENOUS (Freeze-dried powder for intravenous injection)

with **WATER FOR INJECTION – EPILIM®** (Solvent ampoule)

COMPOSITION:

- 1. EPILIM LIQUID SUGAR-FREE:** Each 5 ml contains 200 mg sodium valproate
Preservatives: Sodium methylparabenzoate 0,1 % *m/v* and sodium propylparabenzoate 0,04 % *m/v*.
- 2. EPILIM CR 200:** Each tablet contains 133,2 mg sodium valproate and 58,0 mg valproic acid equivalent to 200 mg sodium valproate.
- 3. EPILIM CR 300:** Each tablet contains 199,8 mg sodium valproate and 87,0 mg valproic acid equivalent to 300 mg sodium valproate.
- 4. EPILIM CR 500:** Each tablet contains 333,0 mg sodium valproate and 145,0 mg valproic acid equivalent to 500 mg sodium valproate.
- 5. EPILIM 100 CRUSHABLE:** Each tablet contains 100 mg sodium valproate.
- 6. EPILIM INTRAVENOUS:** Each vial contains 400 mg freeze-dried sodium valproate
with **WATER FOR INJECTION - EPILIM:** Each ampoule contains 4 ml sterile water for injection.

EPILIM LIQUID SUGAR-FREE excipients:

Sodium methylparabenzoate 0,1 % *m/v* and sodium propylparabenzoate 0,04 % *m/v* as preservatives, as well as cherry flavour, citric acid, hydroxyethylcellulose, Ponceau red colour, saccharin sodium and sorbitol liquid.

EPILIM CR 200, 300 and 500 excipients:

Hypromellose, ethylcellulose, hydrated silica.

Tablet film-coat: Violet coat (Opadry OY-S-6705), containing: hypromellose, titanium dioxide, macrogol 400, indigo carmine aluminium lake FD&C blue No.2, erythrosine BS aluminium lake, iron oxide black.

Sugar free.

EPILIM 100 CRUSHABLE excipients:

Kaolin light (natural), magnesium stearate, maize starch, silica colloidal hydrated.

EPILIM Intravenous excipients with *WATER FOR INJECTION - EPILIM:* N/A

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Sodium valproate has anticonvulsant properties. The exact mode of action is unknown. However, 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.

Pharmacokinetic properties:

Peak plasma concentrations are observed in 1 to 4 hours after sodium valproate liquid, but this can be delayed for several hours if valproic acid is administered in enteric-coated tablets, in prolonged release formulation, or is ingested with meals.

Sodium valproate bioavailability is close to 100 % following oral or IV administration.

Valproic acid concentration in cerebrospinal fluid is close to free plasma concentration.

Steady state plasma concentration is reached after 3 to 4 days, following oral administration.

Valproate is highly bound to plasma proteins; protein binding is dose-dependent and saturable.

When given in therapeutic doses, most of the medicine is converted to the conjugate ester of glucuronic acid, while mitochondrial metabolism, principally by means of beta-oxidation, accounts for the remainder. Some of the metabolites have anticonvulsant activity.

Sodium valproate is mainly excreted in urine following metabolism via glucuro-conjugation and beta-oxidation.

Sodium valproate does not increase its own degradation neither that of other agents such as oestrogen- and progestogen-containing medicines.

The elimination half-life of sodium valproate varies from approximately 8 to 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 in epilepsy is considered to be between 30 and 100 µg/ml. 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 total plasma levels.

The pharmacological (or therapeutic) effects of EPILIM are not clearly correlated with the total or free (unbound) plasma valproic acid levels.

In cases where measurement of plasma levels is considered necessary, trough plasma levels should be used for therapeutic monitoring.

INDICATIONS:

In the treatment of generalised epilepsy, particularly with the following patterns of seizures:

- absence
- myoclonic
- tonic-clonic
- atonic
- mixed.

As well as, for partial epilepsy:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut).

EPILIM CR for the treatment and prevention of mania associated with bipolar disorders.

EPILIM INTRAVENOUS is indicated in patients for whom oral therapy is temporarily not possible.

CONTRAINDICATIONS:

- Hypersensitivity to sodium valproate.
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- Active liver disease, including the following:
 - acute hepatitis
 - chronic hepatitis
 - personal or family history of hepatic dysfunction especially drug-related
 - hepatic porphyria.

WARNINGS:

Liver dysfunction:

Conditions of occurrence:

Cases of severe liver damage resulting sometimes in fatalities have been reported.

Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease. After the age of 3, the incidence of occurrence is reduced and decreases with age. In most cases, such liver damage occurred during the first 6 months of therapy.

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 (see above *CONDITIONS OF OCCURRENCE*):

- Non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- In patients with epilepsy, recurrence of seizures.

Patients (or their family, in the case of 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 performed before and then periodically monitored during the first 6 months of therapy. 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 EPILIM 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.

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been rarely reported. Young children are at particular risk. This risk decreased with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

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 medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

INTERACTIONS:

Effects of EPILIM on other medicines:

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

EPILIM may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore clinical monitoring is advised and dosage should be adjusted when appropriate.

Phenobarbital

EPILIM 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

EPILIM 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

EPILIM decreases phenytoin total plasma concentration. Moreover, EPILIM increases phenytoin free form with possible overdose 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 EPILIM was administered with carbamazepine as valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

EPILIM may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. There are suggestions, yet to be proven, that the risk of rash may be increased by co-administration of lamotrigine with EPILIM.

Zidovudine

EPILIM may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Effects of other medicines on EPILIM:

Antidepressants and neuroleptics may antagonise the anti-epileptic activity of EPILIM by lowering the seizure threshold. This may require EPILIM dosage adjustments.

Anti-epileptics with enzyme inducing effect (including **phenytoin, phenobarbital, carbamazepine**) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of **felbamate** and EPILIM may increase valproate serum concentration. Valproate dosage should be monitored.

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore, epileptic seizures may occur in cases of combined therapy.

Chloroquine may also lower the seizure threshold.

In case of concomitant use of EPILIM and **highly protein bound agents (aspirin)**, valproate free serum levels may be increased.

Close monitoring of INR should be performed in case of concomitant use of **vitamin K dependent factor anticoagulants** (e.g. warfarin and other coumarin anticoagulants) because the anticoagulant effect of these agents may be increased due to displacement from plasma protein binding sites by EPILIM.

Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with **cimetidine** or **erythromycin**.

Carbapenem antibiotics (imipenem/meropenem/ertapenem): decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

Other interactions:

EPILIM usually has no enzyme inducing effect; as a consequence, EPILIM does not reduce efficacy of oestrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

PREGNANCY AND LACTATION:

Pregnancy:

From experience in treated epileptic mothers, the risk associated with the use of EPILIM during pregnancy has been described as follows:

Risk associated with epilepsy and anti-epileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in case of multiple medicine therapy, the respective part of treatments and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations.

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or anti-epileptic treatment.

Notwithstanding those potential risks, 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 fetus.

Risk associated with sodium valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

Pregnant women should not use EPILIM.

Risk in the neonate

Cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken EPILIM during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia; afibrinogenaemia has also been reported and may be fatal. Hypofibrinogenaemia is possibly associated with decrease of coagulation factors.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation:

EPILIM crosses the placenta. When given to breastfeeding mothers, EPILIM is excreted in breast milk.

Excretion of valproate in breast milk results in a concentration between 1 % and 10 % of maternal serum levels.

DOSAGE AND DIRECTIONS FOR USE:

EPILIM LIQUID SUGAR-FREE, EPILIM 100 CRUSHABLE and EPILIM CR 200, 300 and 500 tablets are for oral administration.

EPILIM should preferably be taken with or after food. The tablets should be swallowed whole, if necessary with a little water (but not with aerated mineral water) and not crushed or chewed.

EPILIM 100 CRUSHABLE tablets may be crushed and mixed with food or drinks.

EPILIM LIQUID SUGAR-FREE should not be diluted. EPILIM LIQUID SUGAR-FREE should be given in divided doses.

EPILIM CR is a controlled release formulation of EPILIM, which reduces peak concentration and ensures a more even plasma concentration throughout the day.

EPILIM CR may be given once or twice daily. Daily dosage requirements vary according to age and body weight. In patients where adequate control has been achieved, EPILIM CR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Adults:

Dosage should start at 600 mg/day, where applicable in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range of 1 000 to 2 000 mg/day (i.e. 20-30 mg/kg body mass). If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day, or one other anti-epileptic agent may be added at a low dosage. In patients already receiving other therapy, the same pattern should be followed. If increased sedation is observed, dosage of barbiturates or benzodiazepines (e.g. lorazepam) should be reduced as that of EPILIM is increased; dosage of both EPILIM and other agents should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with EPILIM alone.

Children over 20 kg:

Initial dosage should be 400 mg/day irrespective of mass, where applicable in divided doses, with spaced increases until control is achieved. This is usually within the range of 20 to 30 mg/kg of body mass per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per day.

Children under 20 kg:

20 mg/kg of body mass per day; in severe cases, this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

EPILIM CR for the treatment and prevention of mania associated with bipolar disorders:

The recommended initial dose is 1 000 mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effect.

Doses should be adjusted according to individual clinical response.

Prophylactic treatment should be established individually with the lowest effective dose.

EPILIM INTRAVENOUS:

To reconstitute, inject the solvent provided (4 ml of *WATER FOR INJECTION - EPILIM*) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate, the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of EPILIM INTRAVENOUS is for single dose injection only. EPILIM INTRAVENOUS should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion must be discarded.

EPILIM INTRAVENOUS may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5 %, or dextrose saline.

EPILIM INTRAVENOUS should not be administered via the same IV line as other IV additives.

The intravenous solution is suitable for infusion in PVC, polyethylene, or glass containers.

Patients already satisfactorily treated with EPILIM may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3 - 5 minutes, usually 400 - 800 mg depending on body mass (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2 500 mg/day.

EPILIM INTRAVENOUS should be replaced by oral EPILIM therapy as soon as practicable.

Daily requirement for children is usually in the range of 20 – 30 mg/kg/day and method of administration is as above.

Use in the elderly:

Although the pharmacokinetics of EPILIM is modified in the elderly, this is of 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 dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see PHARMACOKINETIC PROPERTIES).

Combined therapy:

When starting EPILIM in patients already on other anticonvulsants, these should be tapered slowly; initiation of EPILIM 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 10 mg/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, or if side effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of EPILIM. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations:

The concentration of valproate in plasma that appears to be associated with therapeutic effects is approximately 30 – 100 µg/ml. 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 (see PHARMACOKINETIC PROPERTIES).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects:

Where applicable, the following frequency rating has been used:

Very common ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1\ 000$; $< 1/100$); rare ($\geq 1/10\ 000$; $< 1/1\ 000$); very rare ($\leq 1/10\ 000$), including "isolated reports".

Congenital and familial/genetic disorders:

(see PREGNANCY AND LACTATION)

Hepato-biliary disorders:

Rare: cases of liver dysfunction (see WARNINGS)

Gastrointestinal disorders:

Frequent: nausea, gastralgia, diarrhoea occurs in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment

Very rare: cases of pancreatitis, sometimes lethal, have been reported (see WARNINGS)

Nervous system disorders:

Less frequent: confusion; a few cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage.

These cases have most often been reported during combined therapy (in particular with phenobarbital) or after a sudden increase in valproate doses. Cases of reversible dementia associated with reversible cerebral atrophy have been reported. Isolated reversible Parkinsonism has been reported. Transient and/or dose-related fine postural tremor and somnolence have often been reported

Frequent: cases of isolated and moderate hyperammonaemia without change in liver function tests may occur and should not cause treatment discontinuation.

Hyperammonaemia associated with neurological symptoms have also been reported. In such cases further investigations should be considered (see SPECIAL PRECAUTIONS)

Blood and lymphatic system disorders:

Frequent: occurrences of thrombocytopenia

Rare: cases of anaemia, leucopenia or pancytopenia have been reported

Less frequent: isolated reduction of fibrinogen or increase in bleeding time has been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation) (see also PREGNANCY)

Skin and subcutaneous tissue disorders:

Less frequent: cutaneous reactions may occur with valproate such as exanthematous rash. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme have been reported

Frequent: transient and/or dose-related hair loss has often been reported. Regrowth normally begins within six months, although the hair may become curlier than previously

Reproductive system disorders:

Less frequent: amenorrhoea and irregular periods have been reported

Vascular disorders:

Less frequent: the occurrence of vasculitis has been reported

Ear disorders:

Rare: hearing loss, either reversible or irreversible, however a cause and effect relationship has not been established

Renal and urinary disorders:

Less frequent: there have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function) associated with valproate therapy but the mode of action is as yet unclear

Immune system disorders:

Less frequent: allergic reactions have been reported

General disorders and administration site conditions:

Very rare: cases of non-severe peripheral oedema have been reported

Frequent: increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored (see SPECIAL PRECAUTIONS)

Frequencies unknown: when using EPILIM intravenously, nausea or dizziness may occur a few minutes after injection; they disappear spontaneously within a few minutes

Special Precautions:

- Liver function tests should be carried out before therapy (see CONTRAINDICATIONS), and periodically during the first 6 months especially in patients at risk (see WARNINGS).
Increased liver enzymes may be noted, particularly at the beginning of therapy; they are transient and isolated, without clinical sign.
More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

- Monotherapy is recommended in children under the age of 3 years when prescribing EPILIM, but the potential benefit of EPILIM should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see WARNINGS).

The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.

- 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 (see SIDE EFFECTS).
- 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 (see PHARMACOKINETIC PROPERTIES).
- Although immune disorders have been only exceptionally noted during the use of EPILIM, the potential benefit of EPILIM should be weighed against its potential risk in patients with systemic lupus erythematosus.
- Exceptional cases of pancreatitis have been reported; therefore, patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be interrupted.
- When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

- Patients should be warned of the risk of weight gain at the initiation of therapy; and appropriate strategies should be adopted to minimise it (see SIDE EFFECTS).
- **Diabetic patients:** EPILIM is eliminated mainly through the kidneys, partly in the form of ketone bodies, and this may give false-positive readings in the urine testing of possible diabetics.

Effect on ability to drive and use machines:

Patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see INTERACTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Clinical signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis and impaired respiratory function.

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: gastric lavage (which is useful up to 10 to 12 hours following ingestion), cardiorespiratory monitoring, assisted ventilation and other supportive measures are recommended. Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases.

Deaths have occurred following massive overdose.

IDENTIFICATION:

1. EPILIM LIQUID SUGAR-FREE: a red, cherry flavoured liquid.
2. EPILIM CR 200: oblong, violet, film-coated tablets.
3. EPILIM CR 300: oblong, violet, film-coated tablets.
4. EPILIM CR 500: oblong, violet, film-coated tablets.
5. EPILIM 100 CRUSHABLE: round, white, scored tablets.
6. EPILIM INTRAVENOUS with *WATER FOR INJECTION - EPILIM*: off-white, sterile, freeze-dried powder in a clear glass vial, and clear, colourless, aqueous solvent (*WATER FOR INJECTION - EPILIM*) in a 4 ml clear glass ampoule.

PRESENTATION:

EPILIM LIQUID SUGAR-FREE is available in amber PET or amber glass bottles of 300 ml.

EPILIM CR 200, EPILIM CR 300, EPILIM CR 500 tablets are available in blister packs, consisting of silver aluminium foil sealed to silver formed aluminium foil (polyamide/aluminium/PVC) and packed in printed cardboard cartons containing 56 or 100 tablets.

EPILIM 100 CRUSHABLE tablets are available in blister packs, consisting of silver aluminium foil sealed to silver formed aluminium foil (polyamide/aluminium/PVC) and packed in printed cardboard cartons containing 100 tablets.

EPILIM INTRAVENOUS: 400 mg of freeze-dried sodium valproate in a clear glass vial supplied with an ampoule of 4 ml of solvent (*WATER FOR INJECTION - EPILIM*).

STORAGE INSTRUCTIONS:

The tablets, being hygroscopic and sensitive to light, must be kept in their protective foil until taken. Where possible, blister strips should not be cut.

Both tablets and liquid should be stored at or below 25 °C in a dry place away from direct sunlight.

EPILIM INTRAVENOUS freeze-dried powder should be stored at or below 25 °C.

For intravenous use, the reconstituted solution should be used immediately and any unused portion discarded. If the reconstituted solution is further diluted for use as an infusion solution, the dilute solution may be stored for up to 24 hours if kept at 2 to 8 °C before use, discarding any remaining solution after 24 hours.

Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

EPILIM LIQUID SUGAR-FREE:	J/2.5/148
EPILIM CR 200:	27/2.5/0322
EPILIM CR 300:	Y/2.5/286
EPILIM CR 500:	27/2.5/0323
EPILIM 100 CRUSHABLE:	27/2.5/0500
EPILIM INTRAVENOUS:	Y/2.5/43
<i>WATER FOR INJECTION - EPILIM: Y/34/156</i>	

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd.
2 Bond Street,
Midrand, 1685,
South Africa.

DATE OF PUBLICATION OF THE PACKAGE INSERT:

2 March 2012.

NAMIBIA

Scheduling status: **NS2**

Registration numbers:

EPILIM LIQUID SUGAR-FREE : 90/2.5/001520

EPILIM CR 200 : 05/2.5/0008

EPILIM CR 300 : 05/2.5/0009

EPILIM CR 500 : 05/2.5/0010

EPILIM 100 CRUSHABLE : 05/2.5/0202

EPILIM INTRAVENOUS : 05/2.5/0011

WATER FOR INJECTION – EPILIM : 05/34/0012

BOTSWANA

Scheduling status: **S2**

Registration numbers:

EPILIM LIQUID SUGAR-FREE : BOT0801172

EPILIM CR 200 : BOT0700913

EPILIM CR 300 : BOT0700914

EPILIM CR 500 : BOT0700915

EPILIM 100 CRUSHABLE : BOT0801174

EPILIM INTRAVENOUS : BOT0801173