PROFESSIONAL INFORMATION

EPILIM has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the fetus, resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities.

Exposure to EPILIM *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention-deficit hyperactivity disorder (ADHD).

EPILIM treatment must be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and EPILIM must not be prescribed if the relevant risk minimisation measures/Pregnancy Prevention Programme cannot be implemented and supervised and patients are not committed to adhere to these measures.

SCHEDULING STATUS

S3 EPILIM CR 200, EPILIM CR 300 and EPILIM CR 500

S3 EPILIM 100 CRUSHABLE

S3 EPILIM LIQUID SUGAR-FREE

S3 EPILIM INTRAVENOUS

S1 Water for Injection – EPILIM

1. NAME OF THE MEDICINE

EPILIM® CR 200 prolonged-release tablets

EPILIM® CR 300 prolonged-release tablets

EPILIM® CR 500 prolonged-release tablets

EPILIM® 100 CRUSHABLE tablets

EPILIM® LIQUID SUGAR-FREE liquid

EPILIM® INTRAVENOUS freeze-dried powder for intravenous injection/infusion

Water for Injection – EPILIM (solvent ampoule).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPILIM CR 200: Each tablet contains 133,2 mg sodium valproate and 58,0 mg valproic acid, equivalent to 200 mg sodium valproate.

Sugar free.

EPILIM CR 300: Each tablet contains 199,8 mg sodium valproate and 87,0 mg valproic acid, equivalent to 300 mg sodium valproate.

Sugar free.

EPILIM CR 500: Each tablet contains 333,0 mg sodium valproate and 145,0 mg valproic acid, equivalent to 500 mg sodium valproate.

Sugar free.

EPILIM 100 CRUSHABLE: Each tablet contains 100 mg sodium valproate.

Sugar free.

EPILIM LIQUID SUGAR-FREE: Each 5 mL contains 200 mg sodium valproate.

Preservatives: sodium methyl parabenzoate 0,1 % *m/v* and sodium propyl parabenzoate 0,04 % *m/v*.

Contains sorbitol: 925 mg/5 mL.

Contains sweetener: 12,5 mg/5 mL sodium saccharin.

EPILIM INTRAVENOUS: Each vial contains 400 mg freeze-dried sodium valproate.

Water for Injection – EPILIM: Each ampoule contains 4 mL sterile water for injection.

Sugar free.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

EPILIM LIQUID SUGAR-FREE: red, cherry flavoured liquid.

EPILIM CR 200: unmarked oblong, violet, film-coated tablets, nominally 13,25 x 6,75 mm.

EPILIM CR 300: unmarked oblong, violet, film-coated tablets, nominally 15 x 7,5 mm.

EPILIM CR 500: unmarked oblong, violet, film-coated tablets, nominally 17,25 x 9,75 mm.

EPILIM 100 CRUSHABLE: round, white, scored tablets.

EPILIM INTRAVENOUS: off-white, sterile, freeze-dried powder for intravenous injection/infusion.

Water for Injection – EPILIM: clear, colourless, aqueous solvent for re-constitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 in:

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

EPILIM CR is indicated for the acute and maintenance treatment of manic episodes associated with bipolar disorders in adults.

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

4.2 Posology and method of administration

Daily dosage requirements vary according to age and body mass.

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 medicine 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 medicines 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:

Children 20 kg and over

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 – 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 acute and maintenance treatment of manic episodes associated with

bipolar disorders in adults:

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.

Maintenance treatment should be individually established, with the lowest effective dose.

EPILIM INTRAVENOUS:

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 (see Administration below).

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 (see Administration below).

Use in children

Epilepsy indication

Among the oral pharmaceutical forms, the following formulations are more appropriate for administration to children less than 11 years: oral solution and crushable tablets (see Administration below).

Bipolar disorders

In children and adolescents:

The safety and efficacy of EPILIM for the treatment of manic episodes in bipolar disorder have not been established in studies in patients aged less than 18 years (see sections 4.4 and 4.8).

Use in the elderly

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 sections 4.4 and 5.3).

Patients with hepatic insufficiency

Please refer to sections 4.3, 4.4 and 4.8.

Female children, women of childbearing potential and pregnant women

EPILIM must not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. Please refer to sections 4.3, 4.4 and 4.6.

Estrogen-containing products:

EPILIM does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased EPILIM efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (see section 4.5).

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 (phenobarbitone) 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 (especially 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 section 5.2).

Administration

Oral formulations:

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.

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. The tablets should be swallowed whole, if necessary with a little water (but not with

aerated mineral water) and not crushed or chewed.

In view of the sustained release process and the nature of the excipients in the formula of EPILIM CR tablets, the inert matrix is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released.

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

Intravenous formulation:

EPILIM INTRAVENOUS should be reconstituted immediately prior to use. For instructions on reconstitution of EPILIM INTRAVENOUS before administration, see section 6.6. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/mL.

EPILIM INTRAVENOUS may be given by direct slow intravenous injection or by infusion using a separate intravenous line (see section 6.6 for compatibility information).

4.3 Contraindications

- Hypersensitivity to sodium valproate or to any of the formulation components of EPILIM.
- Pregnancy and lactation (see sections 4.4 and 4.6).
  - With the treatment of epilepsy:
    - In pregnancy, unless there is no suitable alternative treatment.
    - In women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled.
  - With the treatment of bipolar disorder:
    - In pregnancy.
    - In women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled.
- Active liver disease, including the following:

- Acute hepatitis.
- Chronic hepatitis.
- Personal or family history of severe hepatitis, especially if medicine related.
- Hepatic porphyria.

- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG, e.g. Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with known urea cycle disorders (see section 4.4).

4.4 Special warnings and precautions for use

Treatment with EPILIM must be initiated and supervised by a medical practitioner experienced in the management of epilepsy and bipolar disorders.

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme:

EPILIM has a high teratogenic potential and children exposed *in utero* to EPILIM have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

EPILIM is contraindicated in the following situations:

- With treatment of epilepsy:
  - in pregnancy, unless there is no suitable alternative treatment (see sections 4.3 and 4.6)
  - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6)
- With treatment of bipolar disorder:
  - in pregnancy (see sections 4.3 and 4.6)
  - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6).

Conditions of the Pregnancy Prevention Programme:

The medical practitioner must ensure that:

- Individual circumstances are evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to EPILIM *in utero.*
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (refer to Contraception in this section), without interruption during the entire duration of treatment with EPILIM.
- The patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy, or bipolar disorders.
- The patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timeous discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- The patient understands the need to urgently consult her medical practitioner in case of pregnancy.
- The patient has received the patient guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with EPILIM use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the medical practitioner considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pharmacists or health care professionals must ensure that:

- The patient card is provided with every EPILIM dispensing and that the patients understand its content.
- Patients are advised not to stop their EPILIM medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Female children:

- The medical practitioner must ensure that parents/caregivers of female children understand the need to contact the medical practitioner once the female child using EPILIM experiences menarche (see section 4.3).
- The medical practitioner must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for infants exposed to EPILIM *in utero* (see section 4.3).
- In patients who experienced menarche, the medical practitioner must reassess the need for EPILIM therapy annually and consider alternative treatment options. If EPILIM is the only suitable treatment, the need for using effective contraception and all other conditions of the Pregnancy Prevention Programme must be discussed. Every effort should be made by the medical practitioner to switch female children on EPILIM to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test:

Pregnancy must be excluded before start of treatment with EPILIM. Treatment with EPILIM must not be initiated in women of childbearing potential without a negative pregnancy test result (plasma pregnancy test), confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception:

Women of childbearing potential who are prescribed EPILIM must use effective contraception without interruption during the entire duration of treatment with EPILIM. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for

contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user-independent form such as an intra-uterine device or implant) or two complementary forms of contraception, which includes a barrier method, should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method, and involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea, she must follow all the advice on effective contraception (see section 4.3).

Estrogen-containing products:
EPILIM does not reduce efficacy of hormonal contraceptives. However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased EPILIM efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (see section 4.5).

Annual treatment reviews by a medical practitioner:
The medical practitioner must at least annually review whether EPILIM is the most suitable treatment for the patient. The medical practitioner should discuss the annual risk acknowledgement form, at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning:
For the indication of epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess EPILIM therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6: Pregnancy).
If switching is not possible, the woman should receive further counselling regarding the EPILIM

risks for the unborn child, to support her informed decision-making regarding family planning (see section 4.3).

For the indication of bipolar disorder, if a woman is planning to become pregnant a medical practitioner experienced in the management of bipolar disorder must be consulted and treatment with EPILIM should be discontinued and, if needed, switched to an alternative treatment prior to conception and before contraception is discontinued (see section 4.3).

In case of pregnancy:

If a woman using EPILIM becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with EPILIM and consider alternative options. Patients with an EPILIM-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see sections 4.3 and 4.6: Pregnancy).

Educational materials:

In order to assist health care professionals and patients in avoiding exposure to EPILIM during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of EPILIM in women of childbearing potential and includes the details of the Pregnancy Prevention Programme. A patient guide and patient card should be provided to all women of childbearing potential using EPILIM (see section 4.3).

An annual risk acknowledgement form needs to be completed at time of treatment initiation and during each annual review of EPILIM treatment by the medical practitioner.

Children (male and female) less than 18 years of age:

Epilepsy:

Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving EPILIM (see section 4.8). Current evidence is inconclusive as to the possibility of

harm to reproductive organs, skeletal system growth or developing brain of patients less than 18 years of age.

In male children less than 18 years of age, EPILIM should be used with caution and in alignment with guidelines on the use of antiepileptics.

EPILIM can be used in female children less than 18 years of age only if there is no suitable safer alternative therapy or alternate therapy have failed to control the epilepsy. In addition, for female children, ensure that the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6: Pregnancy).

Bipolar disorder:
EPILIM is not indicated for the treatment of manic episodes in bipolar disorder in children (see section 4.1).

Adult males intending procreation:
EPILIM has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see sections 4.6 and 4.8). The medical practitioner should discuss with adult males their intent to procreate, when prescribing EPILIM. If procreation is intended, EPILIM should be used only if alternative treatment options are not suitable.

Severe liver damage:
Conditions of occurrence:
Cases of severe liver damage, which may result 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 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3 years, the incidence of occurrence is reduced and decreases with age. In most cases, such liver damage occurred during the first 6 months of therapy.

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 section 4.5).

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 and/or 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 any such signs immediately to a medical practitioner should they occur. Investigations, including clinical examination and laboratory assessment of liver function, should be undertaken immediately.

Detection:

Liver function tests should be performed before therapy is initiated and then periodically monitored during the first 6 months of therapy (see section 4.5).

Increased liver enzymes may be noted, particularly at the beginning of therapy. More extensive biological investigations (including prothrombin index/prothrombin time [INR/PT]) are recommended in patients developing increased liver enzymes. An adjustment of dosage (decrease) may be needed when appropriate and tests should be repeated as necessary.

Amongst usual investigations, tests which reflect protein synthesis, particularly INR/PT, are most relevant. Confirmation of an abnormally low INR/PT, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires discontinuation of EPILIM therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued, since they follow the same metabolic pathway.

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

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been reported. Young children are at particular risk. This risk decreases with increasing age. Severe seizures, neurological impairment or concomitant anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, EPILIM should be discontinued.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines, including EPILIM, in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines has also shown an 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.

Carbapenem antibiotics:

The concomitant use of EPILIM and carbapenem antibiotics is not recommended (see section 4.5).

Patients with known or suspected mitochondrial disease:

EPILIM may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear-encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with EPILIM treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG: e.g. Alpers-Huttenlocher syndrome).

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura.

POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Aggravated convulsions:

Some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with EPILIM. In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

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 (see section 4.8).

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 (see sections 4.2 and 5.2).

Systemic lupus erythematosus:

New development and exacerbation of systemic lupus erythematosus (SLE) may occur. The potential benefit of EPILIM should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia:

EPILIM may cause hyperammonaemia.

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with EPILIM (see section 4.3).

Weight gain:

Patients should be warned of the considerable risk of weight gain at the initiation of therapy, and appropriate strategies should be adopted to minimise this (see section 4.8).

Carnitine palmitoyltransferase (CPT) type II deficiency patients:

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking EPILIM.

Diabetic patients:

EPILIM is excreted mainly through the kidneys, partly in the form of ketone bodies, and this may give false positive readings in the urine testing of diabetics.

Alcohol use during treatment with EPILIM:

Alcohol intake is not recommended during treatment with EPILIM.

Sorbitol:

EPILIM LIQUID SUGAR-FREE contains 925 mg sorbitol per 5 mL, which may cause gastrointestinal discomfort and may have a mild laxative effect. Sorbitol is a source of fructose. Patients with intolerance to some sugars or diagnosed with hereditary fructose intolerance (HFI), should not take EPILIM SUGAR-FREE.

4.5 Interactions with other medicines and other forms of interaction

Effects of EPILIM on other medicines:

- ***Neuroleptics, monoamine oxidase (MAO) inhibitors, antidepressants and benzodiazepines:***

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

- ***Phenobarbital (phenobarbitone):***

  EPILIM increases phenobarbital (phenobarbitone) 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 (phenobarbitone) doses if sedation occurs and determination of phenobarbital (phenobarbitone) plasma levels when appropriate.

- ***Primidone:***

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

- ***Phenytoin:***

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

- ***Lamotrigine:***

  The risk of rash may be increased by co-administration of lamotrigine with valproic acid, when lamotrigine is added on to EPILIM. EPILIM may reduce lamotrigine metabolism and increase its mean half-life. Dosages should be adjusted (lamotrigine dosage decreased) when appropriate. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes.

- ***Zidovudine:***

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

- ***Felbamate:***

  EPILIM may decrease the felbamate mean clearance by up to 16 %.

- ***Olanzapine:***

  EPILIM may decrease the olanzapine plasma concentration.

- ***Rufinamide:***

  EPILIM may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, particularly in children, as this effect is larger in this population.

- ***Propofol:***

  EPILIM may lead to an increased blood level of propofol. When co-administered with EPILIM, a reduction of the dose of propofol should be considered.

- ***Nimodipine:***

  Concomitant treatment of nimodipine with EPILIM may increase nimodipine plasma concentration by 50 %.

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:***

  Anti-epileptic medicines with enzyme-inducing effect (including **phenytoin**, **phenobarbital [phenobarbitone]** and **carbamazepine**) decrease valproic acid serum concentrations. Dosages of EPILIM should be adjusted according to clinical response and blood levels in case of combined therapy.

  On the other hand, combination of **felbamate** and EPILIM decreases valproic acid clearance by 22 % to 50 %, and consequently increases the valproic acid plasma concentrations. EPILIM dosage should be monitored.

  Valproic acid metabolite levels may be increased in case of concomitant use with **phenytoin** or **phenobarbital** (phenobarbitone). Therefore, patients treated with any of these two medicines together with EPILIM should be carefully monitored for signs and symptoms of hyperammonaemia.
- ***Mefloquine:***

  Mefloquine increases valproic acid metabolism and epileptic seizures may occur in cases of combined therapy with EPILIM. **Chloroquine** may also lower the seizure threshold.
- ***Highly protein-bound medicines:***

  In case of concomitant use of EPILIM and highly protein-bound medicines (aspirin), valproic acid free serum levels may be increased.
- ***Vitamin K-dependent factor anticoagulants:***

  Close monitoring of INR (prothrombin index) should be performed in case of concomitant use of vitamin K-dependent factor anticoagulants (e.g. warfarin) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by EPILIM.
- ***Cimetidine*** *or* ***erythromycin:***

  Valproic acid serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use of EPILIM with cimetidine or erythromycin.
- ***Carbapenem antibiotics (imipenem/meropenem/ertapenem):***

Decreases in blood levels of valproic acid have been reported when EPILIM is co-administered with carbapenem antibiotics. Co-administration results in a 60 – 100 % decrease in valproic acid levels within two days, sometimes associated with convulsions.

Due to the rapid onset and the extent of the decrease, co-administration of carbapenem antibiotics in patients stabilised on EPILIM should be avoided (see section 4.3). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

- ***Rifampicin:***

  Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, EPILIM dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors:***

  Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma levels when co-administered with EPILIM.

  Although formal interaction studies have not been performed, available data suggest a reduction ranging from 40 % to 77,5 % in valproate plasma levels.

  Patients using protease inhibitors such as ritonavir for the treatment of HIV infection should be carefully monitored for decreased control of their epilepsy/mood status of bipolar patients if also treated with EPILIM.

- ***Colestyramine:***

  Colestyramine may lead to a decrease in plasma levels of valproate when co-administered with EPILIM.

- ***Estrogen-containing medicines:***

  Estrogen-containing medicines, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased EPILIM efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when adding or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels (see section 4.4).

- ***Metamizole:***

Metamizole may decrease valproate serum levels when co-administered with EPILIM, which may result in potentially decreased valproate clinical efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Other interactions:

- ***Risk of liver damage:***

  The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity (see section 4.4).

  Concomitant use of EPILIM and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).

  In patients of all ages receiving cannabidiol at doses 10 to 25 mg/kg and valproate concomitantly, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19 % of patients.
  Appropriate liver monitoring should be exercised when EPILIM is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

- ***Topiramate and acetazolamide:***

  Concomitant administration of EPILIM and topiramate or acetazolamide has been associated with encephalopathy, metabolic acidosis and/or hyperammonaemia. Patients treated with these two medicines should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.

- ***Quetiapine:***

  Co-administration of EPILIM and quetiapine may increase the risk of neutropenia/leucopenia.

- ***Estrogen- and/or progestogen-containing medicines:***

  EPILIM usually has no enzyme-inducing effect. As a consequence, EPILIM does not reduce

efficacy of estrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

4.6 Fertility, pregnancy and lactation

Pregnancy:

EPILIM is contraindicated in pregnancy and lactation (see section 4.3):

- With the treatment of epilepsy:
  - In pregnancy, unless there is no suitable alternative treatment.
- With the treatment of bipolar disorder:
  - EPILIM should not be used in pregnancy for the treatment of bipolar disorder (see section 4.3).

EPILIM is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.

Pregnancy exposure risk related to EPILIM:

Both EPILIM monotherapy and EPILIM polytherapy including other anti-epileptics are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy that includes EPILIM may be associated with a greater risk of congenital malformations than EPILIM monotherapy.

EPILIM was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations:

Data from a meta-analysis (including registries and cohort studies) have shown that 10,73 % of children born to epileptic women exposed to EPILIM monotherapy during pregnancy suffer from congenital malformations (95 % CI: 8,16 – 13,29 %). This is a greater risk of major malformations

than for the general population, for whom the risk is about 2 – 3 %. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor or major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip/palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius) and multiple anomalies involving various body systems.

In utero exposure to EPILIM may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental/neurodevelopmental disorders:
Data have shown that exposure to EPILIM *in utero* can have adverse effects on mental and physical development of the exposed children. This risk appears to be dose dependent, but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of risk throughout the entire pregnancy cannot be excluded.
Studies in preschool children exposed *in utero* to EPILIM show that up to 30 – 40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school-aged children (age 6) with a history of EPILIM exposure *in utero* was on average 7 – 10 points lower than those of children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to EPILIM that the risk of intellectual impairment may be independent from maternal IQ.

Available data from a population-based study show that children exposed to EPILIM *in utero* are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared to the unexposed population in the study.

Available data from another population-based study show that children exposed to EPILIM *in utero* are at increased risk of developing attention-deficit hyperactivity disorder (ADHD) (approximately 1,5-fold) compared to the unexposed population in the study.

In view of the above data the following recommendations should be taken into consideration:
If a woman plans a pregnancy:
For the epilepsy indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision-making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered (see section 4.3).

Pregnant women:
EPILIM as treatment for bipolar disorder is contraindicated for use during pregnancy. EPILIM as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see section 4.3).

If a woman using EPILIM becomes pregnant, she must be referred to a medical practitioner immediately to consider alternative treatment options. During pregnancy, maternal tonic-clonic

seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of EPILIM in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive EPILIM for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of EPILIM into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.
- All patients with an EPILIM-exposed pregnancy and their partners should be referred to a medical practitioner *experienced in teratology/prenatal medicine* for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations.
- If appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may reduce the risk of neural tube defects. However, available evidence does not suggest this prevents the birth defects or malformations due to EPILIM exposure.

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 thrombocytopenia, hypofibrinogenaemia and/or to decrease in other coagulation factors; afibrinogenaemia has also been reported and may be fatal.

  However, this syndrome must be distinguished from the decrease of the vitamin K factors induced by phenobarbital (phenobarbitone) and enzymatic inducers.

  Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken EPILIM during the third trimester of the pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken EPILIM during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken EPILIM during the last trimester of pregnancy.

Fertility:

Amenorrhoea, menstrual disorders, polycystic ovaries, increased testosterone levels, and impairment of ovarian function and of fertility have been reported in female patients using EPILIM (see section 4.8).

EPILIM administration may also impair fertility in male patients (see sections 4.8 and 4.4). Fertility dysfunctions may not always be reversible after treatment discontinuation. Very low concentrations of valproate have been detected in semen of males on treatment with EPILIM.

It is not known with certainty if fertility would be affected by EPILIM treatment in children less than 18 years of age, as valproate may interact with sex hormones.

Breastfeeding:

EPILIM is excreted in breastmilk.

Mothers on EPILIM should not breastfeed their infants (see section 4.3).

Cases of haematological changes and somnolence have been reported in infants of mothers taking EPILIM, when breastfeeding their infants.

4.7 Effects on the ability to drive and use machines

Patients should be warned of the risk of somnolence with EPILIM, and especially in cases of anticonvulsant polytherapy with EPILIM or concomitant treatment of EPILIM with benzodiazepines (see section 4.5).

4.8 Undesirable effects

Where applicable, the following frequency rating has been used:

Very common (≥ 1/10); common (≥ 1/100; < 1/10); uncommon (≥ 1/1 000; < 1/100); rare (≥ 1/10 000; < 1/1 000); very rare (< 1/10 000), including isolated reports.

Neoplasm benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia (see section 4.4)

Uncommon: leucopenia, pancytopenia

Rare: bone marrow failure, including pure red blood cell aplasia, agranulocytosis, macrocytic anaemia, macrocytosis

Isolated reduction of fibrinogen or increase in bleeding time has been reported, usually without associated clinical signs and particularly with high doses (EPILIM has an inhibitory effect on the second phase of platelet aggregation) (see sections 4.4 and 4.6).

Endocrine disorders:

Uncommon: syndrome of inappropriate secretion of ADH (antidiuretic hormone) (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or increased androgen)

Rare: hypothyroidism (see section 4.6)

Metabolism and nutrition disorders:

Common: hyponatraemia, increased weight (see section 4.4)

Rare: hyperammonaemia, obesity

Hyperammonaemia without change in liver function tests may occur and should not cause treatment discontinuation. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered (see section 4.4).

Psychiatric disorders:

Common: confusional state, hallucinations, aggression, agitation*, disturbance in attention*

Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

* These adverse drug reactions are principally observed in the paediatric population.

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, dizziness

Uncommon: coma*, encephalopathy*, lethargy* (see below), parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with cerebral atrophy, cognitive disorder

* Stupor or lethargy sometimes leading to coma/encephalopathy have been described during therapy; this may be associated with an increase in the occurrence of convulsions. These cases have most often been reported during combined therapy (in particular, with phenobarbital [phenobarbitone] or topiramate) or after a sudden increase in EPILIM doses.

Children exposed *in utero:*

Neurodevelopmental problems such as late walking and talking, poor language skills, memory problems, lower intellectual abilities, autistic syndrome and ADHD have been observed in children exposed *in utero* (see section 4.6).

Eye disorders:

Rare: diplopia

Ear and labyrinth disorders:

Common: deafness

Vascular disorders:

Common: haemorrhage (see sections 4.4. and 4.6)

Uncommon: vasculitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion

Gastrointestinal disorders:

Very common: nausea, which may also occur a few minutes after intravenous injection; it usually disappears spontaneously within a few minutes

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, upper abdominal pain, diarrhoea

Uncommon: pancreatitis, which may be fatal (see section 4.4)

Hepato-biliary disorders:

Common: liver injury (see section 4.4)

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, alopecia, nail and nail bed disorders

Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

Musculoskeletal and connective tissue disorders:

Uncommon: bone material density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with EPILIM. The mechanism by which EPILIM affects bone metabolism has not been identified

Rare: development and worsening of systemic lupus erythematosus, rhabdomyolysis

(see section 4.4)

Renal and urinary disorders:

Common: urinary incontinence

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function but the mode of action is, as yet, unclear)

Reproductive system and breast disorders:

Common: dysmenorrhoea

Uncommon: amenorrhoea

Rare: male infertility, polycystic ovaries, impairment of ovarian function and of fertility in females

Congenital and familial and genetic disorders:

Teratogenicity (see section 4.6)

General disorders and administration site conditions:

Uncommon: hypothermia, peripheral oedema

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as increased INR, prolonged prothrombin time, prolonged activated partial thromboplastin time, prolonged thrombin time, biotin deficiency/biotinidase deficiency) (see sections 4.4 and 4.6).

Paediatric population:

The safety profile of EPILIM in the paediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the paediatric population. There is a particular

risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population.

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. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs of acute massive overdose may include coma, with muscular hypotonia, hyporeflexia, miosis and respiratory depression, metabolic acidosis, hypotension and circulatory collapse/shock (also see section 4.8).

Deaths have occurred following massive overdose.

Seizures have been reported in the presence of very high plasma levels of valproate. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the EPILIM formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic and supportive:

Administration of activated charcoal may be useful following ingestion.

Cardiorespiratory monitoring, assisted ventilation and other supportive measures are recommended.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

Naloxone has been used successfully in a few cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics.

A 32.4 Water for injection.

Pharmacotherapeutic group: Anti-epileptics; Fatty acid derivatives. ATC code: N03AG01.

Solvents and diluting agents, including irrigation solutions. ATC code: VO7AB.

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.

5.2 Pharmacokinetic properties

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.

Absorption:

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.

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

Distribution:

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

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.

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

Placental transfer (see section 4.6)

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta, to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism:

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 estrogen- and progestogen-containing medicines.

Elimination:

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 the dosage in accordance with free plasma valproic acid levels.

Paediatric population:
Based on published literature, in paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults. In children aged 2 – 10 years, valproate clearance is 50 % higher than in adults. Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults.

5.3 Preclinical safety data

Genotoxicity:

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay), and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown.

Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus untreated epileptic patients, provided contradictory results.

The biological significance of an increase in SCE frequency is not known.

Carcinogenicity:

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 mg/kg/day and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

Reproductive and developmental toxicity:

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats and rabbits.

In published literature, behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure to clinically relevant doses/exposures of valproate. In mice, behavioural changes have also been observed in the second and third generations, albeit less pronounced in the third generation, following an acute *in utero* exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility:

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 1 250 mg/kg/day and 150 mg/kg/day, respectively.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum

tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to paediatric population is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EPILIM LIQUID SUGAR-FREE:

Sodium methyl parabenzoate 0,1 % *m/v*

Sodium propyl parabenzoate 0,04 % *m/v*

Cherry flavour

Citric acid

Hydroxyethyl cellulose

Ponceau red colourant

Sodium saccharin and sorbitol (see section 2).

EPILIM CR 200, 300 and 500:

Core:

Hypromellose

Ethyl cellulose

Hydrated silica

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.

EPILIM 100 CRUSHABLE:

Kaolin light (natural)

Magnesium stearate

Maize starch

Hydrated silica colloidal.

EPILIM INTRAVENOUS and **Water for Injection – EPILIM:** None.

6.2 Incompatibilities

EPILIM INTRAVENOUS should not be administered via the same IV line as other IV additives (see section 6.6).

6.3 Shelf life

EPILIM LIQUID SUGAR-FREE: 2 years.

EPILIM CR 200, CR 300 and CR 500: 3 years.

EPILIM 100 CRUSHABLE: 3 years.

EPILIM INTRAVENOUS and **Water for Injection – EPILIM** as packaged for sale: 3 years.

EPILIM INTRAVENOUS should be reconstituted immediately prior to use and any unused portion must be 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.

6.4 Special precautions for storage

The tablets, being hygroscopic, 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.

EPILIM INTRAVENOUS and Water for Injection – EPILIM should be stored at or below 30 °C.

Protect from light.

Keep the vial in the carton until required for use.

For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

EPILIM LIQUID SUGAR-FREE is available in amber PET or amber glass bottles of 300 mL and packed together with a leaflet in a printed cardboard carton.

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

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

EPILIM INTRAVENOUS: The freeze-dried powder is packed in a 23 mL clear glass vial with a slotted grey rubber stopper, secured with an aluminium collar and a plastic flip-off cap.

Water for Injection – EPILIM: The 4 mL of solvent is packed in a clear glass ampoule.

1 labelled vial of EPILIM INTRAVENOUS and 1 ampoule of Water for Injection – EPILIM are packed in a cardboard carton with a leaflet.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

Each vial of EPILIM INTRAVENOUS is for single dose injection only. EPILIM INTRAVENOUS should be reconstituted immediately prior to use and any unused portion must be discarded.

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.

EPILIM INTRAVENOUS may be given by direct slow intravenous injection or by infusion using a separate intravenous line in 0,9 % sodium chloride, 5 % dextrose or 2,5 % dextrose/0,45 % sodium chloride.

If the reconstituted solution is further diluted for use as an infusion solution, please refer to storage recommendations in section 6.3.

EPILIM INTRAVENOUS should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene or glass containers.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road

Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBERS

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 LIQUID SUGAR-FREE:	J/2.5/148
EPILIM INTRAVENOUS:	Y/2.5/43
Water for Injection – EPILIM:	Y/34/156

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

EPILIM CR 200:	29 April 1993

EPILIM CR 300:	26 March 1993
EPILIM CR 500:	05 October 1995
EPILIM 100 CRUSHABLE:	24 November 1993
EPILIM LIQUID SUGAR-FREE:	22 August 1978
EPILIM INTRAVENOUS:	13 December 1990
Water for Injection – EPILIM:	18 June 1992

10. DATE OF REVISION OF THE TEXT

10 October 2022

NAMIBIA

Scheduling status: NS2

Registration numbers:

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 LIQUID SUGAR-FREE:	90/2.5/001520
EPILIM INTRAVENOUS:	05/2.5/0011
Water for Injection – EPILIM:	05/34/0012

BOTSWANA

Scheduling status: S2

Registration numbers:

EPILIM CR 200:	BOT0700913
EPILIM CR 300:	BOT0700914
EPILIM CR 500:	BOT0700915
EPILIM 100 CRUSHABLE:	BOT0801174
EPILIM LIQUID SUGAR-FREE:	BOT0801172
EPILIM INTRAVENOUS:	BOT0801173