PROFESSIONAL INFORMATION FOR THE EPILIZINE RANGE

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

EPILIZINE treatment must be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and EPILIZINE 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 EPILIZINE CR 200, EPILIZINE CR 300 and EPILIZINE CR 500

S3 EPILIZINE INTRAVENOUS 400

S1 SOLVENT FOR EPILIZINE INTRAVENOUS

1. NAME OF THE MEDICINE

EPILIZINE® CR 200 prolonged-release tablets

EPILIZINE® CR 300 prolonged-release tablets

EPILIZINE® CR 500 prolonged-release tablets

EPILIZINE® INTRAVENOUS 400 powder for solution for injection/infusion

SOLVENT FOR EPILIZINE INTRAVENOUS solvent for solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Sodium 18,43 mg (see section 4.4).

Sugar free.

EPILIZINE CR 300: Each tablet contains199,8 mg sodium valproate and 87,0 mg valproic acid, equivalent to 300 mg sodium valproate.

Excipients with known effect:

Sodium 27,65 mg (see section 4.4).

Sugar free.

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

Excipients with known effect:

Sodium 46,08 mg (see section 4.4).

Sugar free.

EPILIZINE INTRAVENOUS 400: Each vial contains 400 mg sodium valproate.

Excipients with known effect:

Sodium 55,35 mg (see section 4.4).

SOLVENT FOR EPILIZINE INTRAVENOUS: Each ampoule contains 4 mL sterile water for injection.

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

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

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

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

Powder for solution for injection/infusion.

EPILIZINE INTRAVENOUS 400: Off-white, sterile, freeze-dried, powder for intravenous injection/infusion.

Solvent for solution for injection/infusion.

SOLVENT FOR EPILIZINE INTRAVENOUS: Clear, colourless, aqueous, solvent for reconstitution.

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:

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

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

EPILIZINE INTRAVENOUS 400 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, EPILIZINE 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 EPILIZINE is increased; dosage of both EPILIZINE 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 EPILIZINE 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.

EPILIZINE 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 established individually with the lowest effective dose.

EPILIZINE INTRAVENOUS 400

Patients already satisfactorily treated with EPILIZINE 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).

EPILIZINE INTRAVENOUS 400 should be replaced by oral EPILIZINE 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 EPILIZINE 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 population

The volume of distribution is increased in elderly patients, 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

EPILIZINE must not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6).

Estrogen-containing products

EPILIZINE 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 EPILIZINE 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 EPILIZINE in patients already on other anticonvulsants, these should be tapered slowly. Initiation of EPILIZINE 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 EPILIZINE.

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

EPILIZINE CR 200, EPILIZINE CR 300 and EPILIZINE CR 500 tablets are for oral administration. EPILIZINE should preferably be taken with or after food.

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

Intravenous formulation

EPILIZINE INTRAVENOUS 400 should be reconstituted immediately prior to use. For instructions on reconstitution of EPILIZINE INTRAVENOUS 400 before administration, see section 6.6. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 100 mg/mL.

EPILIZINE INTRAVENOUS 400 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 EPILIZINE (see section 6.1).
- 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 hepatic dysfunction, especially 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).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4 Patients at risk of hypocarnitinaemia).

4.4 Special warnings and precautions for use

Treatment with EPILIZINE 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

EPILIZINE has a high teratogenic potential and children exposed *in utero* to EPILIZINE have a

high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

EPILIZINE 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 EPILIZINE *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 EPILIZINE.
- 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 EPILIZINE 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 providers must ensure that:

- The patient card is provided with every EPILIZINE dispensing and that the patients understand its content.
- Patients are advised not to stop their EPILIZINE 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 EPILIZINE 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 EPILIZINE *in utero* (see section 4.3).
- In patients who experienced menarche, the medical practitioner must reassess the need for

EPILIZINE therapy annually and consider alternative treatment options. If EPILIZINE 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 EPILIZINE to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test:

Pregnancy must be excluded before start of treatment with EPILIZINE. Treatment with EPILIZINE 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 EPILIZINE must use effective contraception without interruption during the entire duration of treatment with EPILIZINE. 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:

EPILIZINE 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 EPILIZINE 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 should at least annually review whether EPILIZINE 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 EPILIZINE 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 EPILIZINE 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 EPILIZINE 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 EPILIZINE becomes pregnant, she must be immediately referred to a medical

practitioner to re-evaluate treatment with EPILIZINE and consider alternative options. Patients with an EPILIZINE exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal 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 providers and patients in avoiding exposure to EPILIZINE during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of EPILIZINE 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 EPILIZINE (see section 4.3).

An Annual Risk Acknowledgement Form needs to be completed at time of treatment initiation and during each annual review of EPILIZINE treatment by the medical practitioner.

Use in male patients:
A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, medical practitioners should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with EPILIZINE should be regularly reviewed by their medical practitioner to evaluate whether EPILIZINE remains the most suitable treatment for the patient. For male patients

planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a medical practitioner experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Educational materials are available for health care providers and male patients. A patient guide should be provided to male patients using valproate.

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 EPILIZINE (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, EPILIZINE should be used with caution and in alignment with guidelines on the use of antiepileptics.

EPILIZINE 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:

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

Adult males intending procreation:

EPILIZINE 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 EPILIZINE. If procreation is intended, EPILIZINE should be used only if alternative treatment options are not suitable.

Severe liver damage:

Conditions of occurrence:

Cases of severe liver damage, sometimes resulting 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 disorders including mitochondrial disorders, such as carnitine deficiency, urea cycle disorders, POLG mutations 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 EPILIZINE, but the potential benefit of EPILIZINE 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, 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 biological assessment of liver function, should be undertaken immediately.

Detection:

Liver function tests should be performed before 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 may be considered 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 cessation of EPILIZINE 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.

Patients with known or suspected mitochondrial disease:

EPILIZINE 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 EPILIZINE 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).

Urea cycle disorders and risk of hyperammonaemia:

EPILIZINE 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 EPILIZINE (see sections 4.3 and 4.4: *Patients at risk of hypocarnitinaemia* and *Severe liver damage*).

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

Patients at risk of hypocarnitinaemia:

EPILIZINE administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonaemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinaemia, when treated with EPILIZINE include patients with metabolic disorders, including mitochondrial disorders related to carnitine (see

warnings on *Patients with known or suspected mitochondrial disease* and *Urea cycle disorders and risk of hyperammonaemia*), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

Patients should be warned to immediately report any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.

Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia should be treated with EPILIZINE only if the benefits of EPILIZINE treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinaemia should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking EPILIZINE. Carnitine supplementation should be considered in these patients (see sections 4.5, 4.8 and 4.9).

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been rarely reported. Young children are at particular risk. The 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. Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, EPILIZINE should be discontinued.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines, including EPILIZINE, 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 EPILIZINE and carbapenem antibiotics is not recommended (see section 4.5).

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 EPILIZINE. 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 EPILIZINE should be weighed against its potential risk in patients with systemic lupus erythematosus.

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 the risk (see section 4.8).

Diabetic patients:

EPILIZINE 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 EPILIZINE:

Alcohol intake is not recommended during treatment with EPILIZINE.

Sodium:

EPILIZINE CR 200 contains 18,43 mg sodium per tablet, equivalent to 0,92 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
EPILIZINE CR 300 contains 27,65 mg sodium per tablet, equivalent to 1,38 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
EPILIZINE CR 500 contains 46,08 mg sodium per tablet, equivalent to 2,30 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
EPILIZINE INTRAVENOUS 400 contains 55,35 mg sodium per vial, equivalent to 2,77 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Effects of EPILIZINE on other medicines:

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

  EPILIZINE 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 (phenobarbitone)***

  EPILIZINE 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***

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

- ***Phenytoin***

  EPILIZINE decreases phenytoin total plasma concentration. Moreover, EPILIZINE 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 EPILIZINE 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***

  The risk of rash may be increased by co-administration of lamotrigine with valproic acid, when lamotrigine is added on to EPILIZINE. EPILIZINE 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***

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

- ***Felbamate***

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

- ***Olanzapine***

  EPILIZINE may decrease the olanzapine plasma concentration.

- ***Rufinamide***

  EPILIZINE 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***

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

- ***Nimodipine***

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

Effects of other medicines on EPILIZINE:

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

- ***Anti-epileptics***

  Anti-epileptics with enzyme-inducing effect (including **phenytoin, phenobarbital [phenobarbitone]** and **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 EPILIZINE decreases valproic acid clearance by 22 % to 50 %, and consequently increases the valproic acid plasma concentrations. EPILIZINE 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 these two medicines should be carefully monitored for signs and symptoms of hyperammonaemia.

- ***Mefloquine***

  Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore, epileptic seizures may occur in cases of combined therapy with EPILIZINE. **Chloroquine** may also lower the seizure threshold.

- ***Highly protein-bound medicines (aspirin)***

  In case of concomitant use of EPILIZINE and highly protein-bound medicines (aspirin), valproate free serum levels may be increased.

- ***Vitamin K-dependent factor anticoagulants***

  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 EPILIZINE.

- ***Cimetidine or erythromycin***

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

- ***Carbapenem antibiotics (imipenem/meropenem/ertapenem)***

  Decreases in blood levels of valproic acid have been reported when EPILIZINE is co-administered with carbapenem antibiotics. Co-administration results in a 60 % to 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 EPILIZINE 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, EPILIZINE 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 EPILIZINE. 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 EPILIZINE.

- ***Colestyramine***

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

- ***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 EPILIZINE 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 EPILIZINE, 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.

- ***Methotrexate***

  Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. 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 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of EPILIZINE 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 EPILIZINE 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 EPILIZINE 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.

- ***Pivalate-conjugated medicines***

  Concomitant administration of EPILIZINE and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinaemia (see section 4.4: *Patients at risk of hypocarnitinaemia*). Concomitant administration of these medicines with EPILIZINE is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

- ***Quetiapine***

  Co-administration of EPILIZINE and quetiapine may increase the risk of

neutropenia/leucopenia.

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

  EPILIZINE usually has no enzyme-inducing effect. As a consequence, EPILIZINE does not reduce efficacy of estrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment of epilepsy

- EPILIZINE is contraindicated during pregnancy, unless there is no suitable alternative treatment.
- EPILIZINE is contraindicated in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Treatment of bipolar disorder

- EPILIZINE is contraindicated during pregnancy.
- EPILIZINE is contraindicated in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy exposure risk related to EPILIZINE

In females, both EPILIZINE monotherapy and EPILIZINE polytherapy including other anti-epileptics are associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both EPILIZINE monotherapy and polytherapy compared to the population not exposed to EPILIZINE.

EPILIZINE 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

A meta-analysis (including registries and cohort studies) showed that about 11 % of children of epileptic women exposed to EPILIZINE monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2 – 3 %). The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic polytherapy, including EPILIZINE is higher than that of anti-epileptic medicines polytherapy not including EPILIZINE. This risk is dose-dependent in EPILIZINE monotherapy, and available data suggest it is dose-dependent in EPILIZINE polytherapy. However, 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 EPILIZINE 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.

In utero exposure to EPILIZINE may result in eye malformations (including colobomas, microphthalmos). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neurodevelopmental disorders

Data have shown that exposure to EPILIZINE *in utero* can have adverse effects on mental and physical development of the exposed children. This risk of neurodevelopmental disorders

(including that of autism) seems to be dose-dependent when EPILIZINE is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When EPILIZINE is administered in polytherapy with other anti-epileptic medicines during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.

The exact gestational period of risk for these effects is uncertain and the possibility of risk throughout the entire pregnancy cannot be excluded.

When EPILIZINE is administered in monotherapy, studies in preschool children exposed *in utero* to EPILIZINE 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 EPILIZINE 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 EPILIZINE that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long-term outcomes.

Available data from a population-based study show that children exposed to EPILIZINE *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 EPILIZINE *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 EPILIZINE 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 EPILIZINE 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 EPILIZINE 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:

EPILIZINE as treatment for bipolar disorder is contraindicated for use during pregnancy.

EPILIZINE as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see section 4.3).

If a woman using EPILIZINE 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 EPILIZINE in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive EPILIZINE for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of EPILIZINE 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 EPILIZINE-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal 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 EPILIZINE exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken EPILIZINE 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 EPILIZINE during the third trimester of the pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken EPILIZINE 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 EPILIZINE during the last trimester of pregnancy.

Males and potential risk of neuro-developmental disorders in children of fathers treated with EPILIZINE in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1,50 (95 % CI : 1,09 – 2,07). The adjusted cumulative risk of NDDs ranged between 4,0 % and 5,6 % in the valproate group versus between 2,3 % and 3,2 % in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDDs subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5,0 and 9,2 years compared to 4,8 and 6,6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e. allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, medical practitioners should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with EPILIZINE should be regularly reviewed by their medical practitioner to evaluate whether EPILIZINE is the most suitable treatment for the patient. For male patients

planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a medical practitioner experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.

Breastfeeding

EPILIZINE is excreted in breast milk.

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

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

Fertility

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

EPILIZINE 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 EPILIZINE.

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

4.7 Effects on ability to drive and use machines

Patients should be warned of the risk of somnolence with EPILIZINE, and especially in cases of anticonvulsant polytherapy with EPILIZINE or concomitant treatment of EPILIZINE 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).

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 (EPILIZINE 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: *Urea cycle disorders and risk of hyperammonaemia* and *Patients at risk of hypocarnitinaemia*).

Not known: hypocarnitinaemia (see sections 4.3 and 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 EPILIZINE 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 EPILIZINE. The mechanism by which EPILIZINE 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's 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).

Not known: acquired Pelger-Huet anomaly*

* Acquired Pelger-Huet anomaly has been reported in cases with and without myelodysplastic syndrome.

Paediatric population:

The safety profile of EPILIZINE 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 requested 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs of acute massive overdose may include a 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. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the EPILIZINE 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 measures are recommended.

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

In case of EPILIZINE overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.

Naloxone has been successfully used in a few isolated 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 EPILIZINE 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 nor that of other medicines 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

EPILIZINE CR 200, EPILIZINE CR 300 and EPILIZINE CR 500:

Core:

Hypromellose

Ethyl cellulose

Hydrated silica

Film-coat:

Violet coat containing: hypromellose, titanium dioxide (E171), macrogol 400, indigo carmine aluminium lake FD&C Blue No. 2 (E132), erythrosine BS aluminium lake (E127), iron oxide black (E172).

EPILIZINE INTRAVENOUS with **SOLVENT FOR EPILIZINE INTRAVENOUS:** None.

6.2 Incompatibilities

EPILIZINE INTRAVENOUS 400 should not be administered via the same IV line as other IV additives (see section 6.6).

6.3 Shelf life

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

EPILIZINE INTRAVENOUS 400 and SOLVENT FOR EPILIZINE INTRAVENOUS as packaged for sale: 3 years.

EPILIZINE INTRAVENOUS 400 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

Store EPILIZINE CR tablets at or below 25 °C in a dry place. The tablets, being hygroscopic, must be kept in their protective foil until taken. Where possible, blister strips should not be cut.

EPILIZINE INTRAVENOUS 400 and SOLVENT FOR EPILIZINE INTRAVENOUS 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

EPILIZINE CR 200, EPILIZINE CR 300 and EPILIZINE 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 of 56 or 100 tablets.

EPILIZINE INTRAVENOUS 400: 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.

SOLVENT FOR EPILIZINE INTRAVENOUS: The 4 mL of solvent is packed in a clear glass ampoule.

1 labelled vial of EPILIZINE INTRAVENOUS 400 and 1 ampoule of SOLVENT FOR EPILIZINE INTRAVENOUS 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 EPILIZINE INTRAVENOUS 400 is for single dose injection only.

EPILIZINE INTRAVENOUS 400 should be reconstituted immediately prior to use and any unused portion must be discarded (see section 6.3).

To reconstitute, inject the solvent provided (4 mL of SOLVENT FOR EPILIZINE INTRAVENOUS) 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 100 mg/mL.

EPILIZINE INTRAVENOUS 400 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.

EPILIZINE INTRAVENOUS 400 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
Tel: 011 256 3700

8. REGISTRATION NUMBERS

EPILIZINE CR 200:	A39/2.5/0038
EPILIZINE CR 300:	A39/2.5/0039
EPILIZINE CR 500:	A39/2.5/0040
EPILIZINE INTRAVENOUS 400:	A40/2.5/0699
SOLVENT FOR EPILIZINE INTRAVENOUS:	A40/34/0781

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

EPILIZINE CR 200:	04 December 2009
EPILIZINE CR 300:	04 December 2009
EPILIZINE CR 500:	04 December 2009
EPILIZINE INTRAVENOUS 400:	09 October 2009
SOLVENT FOR EPILIZINE INTRAVENOUS:	09 October 2009

10. DATE OF REVISION OF THE TEXT

02 April 2025

NAMIBIA

Scheduling status: NS2

Registration numbers:

EPILIZINE CR 200: 16/2.5/0192

EPILIZINE CR 300: 16/2.5/0191

EPILIZINE CR 500: 16/2.5/0190