PROFESSIONAL INFORMATION

EVALEX™ IV 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 foetus 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 EVALEX IV *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD). EVALEX IV treatment should be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy and EVALEX IV should 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 (see sections 4.4 and 4.6).

SCHEDULING STATUS: S3

1. Name of the medicine

EVALEX™ 300 mg IV

EVALEX™ 400 mg IV

EVALEX™ 1 g IV

Solution for infusion or injection (100 mg/ml)

2. Qualitative and quantitative composition

EVALEX IV contains sodium valproate 100 mg/ml.

Each 3 ml ampoule contains 300 mg sodium valproate.

Each 4 ml ampoule contains 400 mg sodium valproate.

Each 10 ml ampoule contains 1 000 mg sodium valproate.

Sugar free.

Excipient with known effect:

Sodium

EVALEX 300 mg IV contains 1,93 mmol (44,5 mg) sodium in each 3 ml ampoule.

EVALEX 400 mg IV contains 2,57 mmol (59,2 mg) sodium in each 4 ml ampoule.

EVALEX 1 g IV contains 6,44 mmol (148,2 mg) sodium in each 10 ml ampoule.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection or infusion.

A clear colourless solution, free from particles.

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).

For the treatment and prevention of mania associated with bipolar disorders.

EVALEX IV is indicated in patients for whom oral therapy is temporarily not possible.

4.2 Posology and method of administration

Posology

Daily dosage requirements vary according to age and body weight. Doses should be adjusted according to individual clinical response.

Adults:

Patients already satisfactorily treated with an oral valproate product 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.

EVALEX IV should be replaced by oral valproate therapy as soon as practicable.

Combined therapy:

When starting EVALEX IV in patients already on other anticonvulsants, these should be tapered slowly. Initiation of EVALEX IV therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases, it may be necessary to increase the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants that 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 EVALEX IV. When barbiturates are being administered concomitantly and particularly if sedation is observed, 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).

Special populations

Elderly patients (65 years and older):

Although the pharmacokinetics of sodium valproate is modified in the elderly, this is of limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly, and, because of decreased binding to serum albumin, the proportion of free medicine is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency:

It may be necessary to decrease the dosage. The dosage should be adjusted according to clinical monitoring, since plasma concentrations may be misleading (see section 5.2).

Paediatric population

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

Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per day. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Method of administration:

EVALEX IV may be given by direct slow intravenous injection or by infusion.

EVALEX IV should not be administered via the same intravenous line with other IV additives.

EVALEX IV solution for injection may be given directly by slow intravenous injection, over 3 – 5 minutes, or by infusion using a separate intravenous line in 0,9 % sodium chloride solution for infusion, 5 % dextrose solution for infusion or Ringer's solution for infusion, see section 6.6.

Prior to use EVALEX IV and the diluted solution should be visually inspected. Only clear solutions without particles should be used.

The contents of the ampoule are for single use only. Any remaining solution should be discarded.

4.3 Contraindications

- Hypersensitivity to sodium valproate or any of the ingredients of EVALEX IV (see section 6.1).
- 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 the 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).
- In pregnancy and lactation (see sections 4.4 and 4.6).

- For treatment of epilepsy:
    - In pregnancy unless there is no suitable alternative treatment
    - In woman of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Treatment with EVALEX IV should be initiated and supervised by a medical practitioner experienced in the management of epilepsy and bipolar disorder.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. The generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Women of childbearing potential, female children and pregnant women:

Pregnancy Prevention Programme

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

EVALEX IV is contraindicated in the following situations:

- 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).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances are evaluated in each case. Involve 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 valproate *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 (for further details please refer to subsection *Contraception* of this boxed warning), without interruption during the entire duration of treatment with EVALEX IV.
- The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy and bipolar disorder.
- The patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timely 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 Information Leaflet.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use.

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

Female children

The prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate (as in EVALEX IV) experiences menarche.
- The 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 children exposed to valproate (as in EVALEX IV) *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate (as in EVALEX IV) is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

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

Contraception

Women of childbearing potential who are prescribed valproate (as in EVALEX IV) must use effective contraception without interruption during the entire duration of treatment with valproate. 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 including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate (as in EVALEX IV) efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.

Conversely, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist

The specialist should review at least annually whether EVALEX IV is the most suitable treatment for the patient and ensure that appropriate advice is given and understood by the patient.

Pregnancy planning

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess 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 (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using valproate (as in EVALEX IV) becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:

The Patient Information Leaflet is provided with every valproate dispensation and that patients understand its content.

Patients are advised not to stop EVALEX IV and to immediately contact a specialist in case of planned or suspected pregnancy.

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with for the patient by a specialist experienced in the management of epilepsy.

Liver dysfunction:

Conditions of occurrence:

Severe liver damage, including hepatic failure have resulted 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 in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

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

In most cases, such liver damage occurred during the first 6 months of therapy.

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, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the medicine.

Patients (or their family, in the case of children) should be instructed to report immediately any such signs to a medical practitioner should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of EVALEX IV 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.

Increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:

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

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 valproate (as in EVALEX IV). In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. Studies show a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data does not exclude the possibility of an increased risk for sodium valproate (as in EVALEX IV).

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

Carbapenem medicines:

The concomitant use of valproate and carbapenem medicines is not recommended.

Patients with known or suspected mitochondrial disease:

EVALEX IV 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, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the 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).

Haematological tests:

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).

Patients with systemic lupus erythematosus (SLE):

Although immune disorders have only rarely been noted during the use of EVALEX IV, the potential benefit of EVALEX IV should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8). New development and exacerbation of SLE may occur.

Urea cycle disorders:

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

Weight gain:

EVALEX IV frequently causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8).

Diabetic patients:

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

Carnitine palmitoyl transferase (CPT) type II deficiency:

Patients with an underlying carnitine palmitoyl transferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking EVALEX IV.

Alcohol:

Alcohol intake is not recommended during treatment with valproate.

Adult males intending procreation:

Valproate, as contained in EVALEX IV, 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 EVALEX IV. If procreation is intended, EVALEX IV should be used only if alternative treatment options are not suitable.

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in childrenborn 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, GPs and specialists should inform male patients about this potential risk (see section 4.6)and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

EVALEX IV contains sodium (see section 2).

EVALEX 300 mg IV contains 1,93 mmol (44,5 mg) sodium in each 3 ml ampoule. This is equivalent to 2 % of the recommended maximum daily dietary intake of 2 g sodium for an adult.

EVALEX 400 mg IV contains 2,57 mmol (59,2 mg) sodium in each 4 ml ampoule. This is equivalent to 3 % of the recommended maximum daily dietary intake of 2 g sodium for an adult.

EVALEX 1 g IV contains 6,44 mmol (148,2 mg) sodium in each 10 ml ampoule. This is equivalent to 7 % of the recommended daily dietary intake of 2 g sodium for an adult.

Paediatric population

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

Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving EVALEX IV (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, EVALEX IV should be used with caution and in alignment with guidelines on the use of antiepileptics.

EVALEX IV 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 section 4.4 and 4.6).

4.5 Interaction with other medicines and other forms of interaction

Effects of EVALEX IV on other medicines

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

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

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium

EVALEX IV has no effect on serum lithium levels.

Olanzapine

Valproic acid (as in EVALEX IV) may decrease the olanzapine plasma concentration.

Phenobarbital

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

Primidone

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

Phenytoin

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

Carbamazepine

Clinical toxicity has been reported when EVALEX IV was administered with carbamazepine as EVALEX IV may potentiate toxic effects of

carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

EVALEX IV reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended, and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

Felbamate

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

Rufinamide

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

Propofol

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

Zidovudine

EVALEX IV may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Nimodipine

In patients concomitantly treated with EVALEX IV and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

Temozolomide

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

Effects of other medicines on EVALEX IV

Anti-epileptics

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore, patients treated with those two medicines should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and EVALEX IV decreases valproic acid clearance by 22 – 50 % and consequently increase the valproic acid plasma concentrations. EVALEX IV dosage should be monitored.

Anti-malarial medicines

Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in

cases of combined therapy. Accordingly, the dosage of EVALEX IV may need adjustment.

Highly protein bound medicines

In case of concomitant use of EVALEX IV and highly protein bound medicines (e.g. aspirin), free valproic acid plasma levels may be increased.

Vitamin K-dependent factor anticoagulants

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

Cimetidine or erythromycin

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem medicines resulting 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 medicines in patients stabilised on valproic acid (as in EVALEX IV) should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Rifampicin

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

Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered.

Cholestyramine

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

Conversely, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative medicines in women receiving hormonal contraception.

Metamizole

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

Other interactions

Caution is advised when using EVALEX IV in combination with newer anti-epileptics whose pharmacodynamics may not be well established. Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two medicines, careful monitoring of signs and symptoms is advised particularly in at risk patients such as those with pre-existing encephalopathy.

Quetiapine

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

4.6 Fertility, pregnancy and lactation

Pregnancy

EVALEX IV is contraindicated in pregnancy and lactation (see section 4.3).

EVALEX IV should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4).

EVALEX IV is contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.

Both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy

including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

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

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and 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 valproate may also result in hearing impairment or deafness 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 did not recover.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations.

Developmental problems/Neurodevelopmental disorders

Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk seems 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 a risk throughout the entire pregnancy cannot be excluded.

Developmental problems have been reported in up to 30 to 40 % of pre-school children exposed to valproate (as contained in EVALEX IV) *in utero*, including delays in early development such as walking and talking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Children exposed to valproate in the womb are also at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).

Other risks in the neonate

Haemorrhagic syndrome has been reported in neonates whose mothers have taken EVALEX IV during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors; afibrinogenemia 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 and other anti-epileptic enzyme inducing medicines.

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 valproate (as in EVALEX IV) during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have received valproate (as in EVALEX IV) during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Female children and woman of childbearing potential (see above and section 4.4)

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess 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 (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be

immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate 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 valproate-exposed pregnancy and their partners should be referred to a specialist experienced in 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. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Breastfeeding

Valproate is excreted in human milk with a concentration ranging from 1-10 % of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8). EVALEX IV should not be used during lactation (see section 4.3).

Fertility

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

Valproate (as in EVALEX IV) administration may also impair fertility in men (see section 4.8). Case reports indicate that 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 valproate.

It is not known with certainty if fertility would be affected by valproate 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 transient drowsiness with EVALEX IV, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5 and 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions:

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Less frequent: Myelodysplastic syndrome

Blood and lymphatic system disorders

Frequent: Anaemia, thrombocytopenia (see section 4.4)

Less frequent:	Pancytopenia, leucopenia, bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis, reduction in blood fibrinogen, spontaneous bruising, bleeding (indication for withdrawal of medication pending investigation, see section 4.4, *Haematological precautions* and section 4.6)

Immune system disorders

Frequent:	Hypersensitivity
Less frequent:	Angioedema

Endocrine disorders

Less frequent:	Syndrome of inappropriate secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase), hypothyroidism (see section 4.6, *Risk in the neonate)*

Metabolic and nutrition disorders

Frequent:	Hyponatraemia, weight gain (risk factor for polycystic ovary syndrome, see section 4.4)
Less frequent:	Hyperammonaemia* (see section 4.4), obesity

* Hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur valproate should be discontinued.

Psychiatric disorders

Frequent:	Confusional state, hallucinations, aggression, agitation, disturbance in attention
Less frequent:	Abnormal behaviour, reversible dementia associated with cerebral atrophy, psychomotor hyperactivity, learning disorder

Nervous system disorders

Frequent:	Extrapyramidal disorder, stupor, convulsion, memory impairment, tremor, headache, dizziness, nystagmus, somnolence
Less frequent:	Encephalopathy**, lethargy, reversible parkinsonism, ataxia, paraesthesia, increased alertness, coma**, aggravated convulsions (see section 4.4), reversible dementia associated with reversible cerebral atrophy, cognitive disorder, sedation, lethargy

progressing to stupor**, which may be associated with hallucinations or convulsions

** These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Eye disorders

Less frequent: Diplopia

Ear and labyrinth disorders

Frequent: Deafness

Vascular disorders

Frequent: Haemorrhage (see sections 4.4 and 4.6)

Less frequent: Vasculitis

Respiratory, thoracic and mediastinal disorders

Less frequent: Pleural effusion

Gastro-intestinal disorders

Frequent: Diarrhoea, nausea, vomiting, indigestion, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia

Less frequent: Pancreatitis (which may be fatal)

Hepato-biliary disorders

Frequent: Liver injury, hepatic failure, sometimes

resulting in death, increased liver enzymes (see 4.2, 4.3 and 4.4)

Skin and subcutaneous tissue disorders

Frequent: Alopecia, nail and nail bed disorders

Less frequent: Skin rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Musculoskeletal, connective tissue and bone disorders

Less frequent: Systemic lupus erythematosus, bone mineral density decreased, osteopenia, osteoporosis, fractures in patients on long-term treatment with EVALEX IV, rhabdomyolysis (see section 4.4)

Renal and urinary disorders

Frequent: Urinary incontinence

Less frequent: Renal failure, enuresis, tubulointerstitial nephritis reversible, Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria)

Frequency unknown: Urine ketone test: false-positive results

Reproductive system and breast disorders

Frequent:	Dysmenorrhoea
Less frequent:	Amenorrhoea, gynaecomastia, irregular periods, male infertility, polycystic ovaries, impairment of ovarian function and fertility in females

Congenital and familial/genetic disorders

Frequency unknown:	Congenital malformations and developmental disorders (see section 4.4 and 4.6)

General disorders and administration site disorders

Less frequent:	Hypothermia, non-severe peripheral oedema

Investigations

Less frequent:	Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some side effects 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. Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"**Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. Deaths have occurred following massive overdose.

Symptoms may however be variable, and seizures have been reported in the presence of very high plasma levels (see also section 5.2

Pharmacokinetic Properties). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Treatment

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring, assisted ventilation and other supportive measures.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group:

Anti-epileptics; Fatty acid derivatives, ATC code: N03AG01

Sodium valproate is an anticonvulsant. 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 between 30 and 100 µg/ml. This reported range may depend on time of sampling and presence of other medicines. The

percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels.

The pharmacological (or therapeutic) effects of sodium valproate 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.

Absorption

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

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

Distribution

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

Biotransformation

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 crosses the placental barrier (see section 4.6).

Elimination

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

Sodium valproate does not increase its own degradation, neither that of other medicines containing oestrogen and progestogen.

The elimination half-life of sodium valproate varies from approximately 8 to 20 hours. It is usually shorter in children.

Renal impairment

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

Paediatric population

Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. 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 and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1-67 hours. In children aged 2 to 10 years, valproate clearance is 50 % higher than in adults.

6. Pharmaceutical particulars

6.1 List of excipients

Potassium dihydrogen phosphate (buffer)

Disodium phosphate dodecahydrate (buffer)

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

48 months as unopened ampoule.

24 hours after dilution for use as infusion solution (see section 6.4 and 6.6).

6.4 Special precautions for storage

Store at or below 25 °C. Keep ampoules in their original package until required for use.

The contents of the ampoule are for single use only.

After dilution for infusion:

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

The clear solution for injection or infusion is packed in type I transparent glass ampoules in a carton containing 1, 4, 5 or 10 ampoules.

EVALEX 300 mg IV: 3 ml of solution is packed in a 5 ml capacity ampoule.

EVALEX 400 mg IV: 4 ml of solution is packed in a 5 ml capacity ampoule.

EVALEX 1 g IV: 10 ml of solution is packed in a 10 ml capacity ampoule.

Not all pack sizes may be marketed at one time.

6.6 Special precautions for disposal and other handling

For infusion, EVALEX IV may be diluted immediately prior to use in 0,9 % sodium chloride solution for infusion, 5 % dextrose for infusion or Ringer's solution, to achieve a final concentration of 2 mg/ml.

The intravenous solution is suitable for infusion in PVC or glass containers. The mixture should be used immediately after preparation.

If storage is necessary, the prepared solution is physically and chemically stable during 24 hours at 2 – 8 °C. From a microbiological point of view, the product should however be used immediately after opening.

7. Holder of the registration certificate

Macleods Pharmaceuticals SA (Pty) Ltd

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Alberton, South Africa

8. Registration numbers

EVALEX 300 mg IV: 53/2.5/0667

EVALEX 400 mg IV: 53/2.5/0668

EVALEX 1 g IV: 53/2.5/0669

9. Date of first authorisation/renewal of the authorisation

Registration date: 11 July 2023

10. Date of revision of the text

To be determined.