| LABIANA-LIFE SCIENCES, S.A. | Prospecto Evalex 100mg/ml Sudáfrica (ZA) |
|---|---|
| Papel: SPECIALPRINT 40 GR. | Código: 52005917-02 |
| Tintas: P. Negro | ANVERSO |
| Tamaño: 435 X 855 mm | Doblado: 55 x 95 mm, con etiqueta de cierre |
| Código Datamatrix: | Prueba nº: 2 |
| | Fecha: 24/02/25 |

435 mm

855 mm

**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 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.

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 and strengths 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.**
Office Block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext 12, Alberton.
Tel: +27 11 682 1169

**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**

Not applicable.

PM0076-02
52005917-02

| LABIANA-LIFE SCIENCES, S.A. | Prospecto Evalex 100mg/ml Sudáfrica (ZA) |
|---|---|
| Papel: SPECIALPRINT 40 GR. | Código: 52005917-02 |
| Tintas: P. Negro | REVERSO |
| Tamaño: 435 X 855 mm | Doblado: 55 x 95 mm, con etiqueta de cierre |
| Código Datamatrix: | Prueba nº: 2 |
| | Fecha: 24/02/25 |

435 mm

855 mm

**PATIENT INFORMATION LEAFLET**

**Valproate, as in EVALEX™ IV, may cause birth defects and problems with early development of the child if it is given during pregnancy. If you are a female of childbearing age, you should use an effective method of contraception throughout your treatment (see "Pregnancy, breastfeeding and fertility"). Tell your doctor at once if you want to become pregnant or think you might be pregnant. If you are the parent or caregiver of a female child being treated with EVALEX IV, read the section on Pregnancy and breastfeeding in this leaflet carefully.**

**SCHEDULING STATUS: S3**

**EVALEX™ 300 mg IV**
**EVALEX™ 400 mg IV**
**EVALEX™ 1 g IV**

Solution for injection or infusion (100 mg/ml)
Sodium valproate
Sugar free
Contains sodium: 44,5 mg/3 ml; 59,2 mg/4 ml and 148,2 mg/10 ml

**Read all of this leaflet carefully before you are given EVALEX IV**
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, pharmacist, nurse or other healthcare provider.

**What is in this leaflet**

1. What EVALEX IV is and what it is used for
2. What you need to know before you are given EVALEX IV
3. How EVALEX IV will be administered
4. Possible side effects
5. How EVALEX IV will be stored
6. Contents of the pack and other information

**1. What EVALEX IV is and what it is used for**

EVALEX IV contains sodium valproate, which belongs to a group of medicines called antiepileptics. These are used to control epileptic seizures. EVALEX IV solution for injection is used to treat various types of epileptic seizures (fits) when it is not possible to take sodium valproate tablets.
EVALEX IV is also used in mania: where you may feel excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder".

**2. What you need to know before you are given EVALEX IV**

**EVALEX IV should not be administered to you:**
- if you are hypersensitive (allergic) to sodium valproate or any of the ingredients of EVALEX IV (listed in Section 6)
- if you have liver problems, or have a family history of liver problems
- if you suffer from porphyria (a rare condition that affects the breakdown of components of red blood cells)
- if you have a genetic problem causing a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- if you suffer from urea cycle disorder (a certain metabolic disorder)
- if you are pregnant or breastfeeding your baby. See "Warnings and precautions" and "Pregnancy, breastfeeding and fertility".

**Warnings and precautions**

*Talk to your doctor or healthcare provider before you are given EVALEX IV, if you:*
- have diabetes. EVALEX IV may affect the results of urine tests
- have a carnitine palmitoyltransferase type II deficiency, which prevents the body from using certain fats for energy, as you may be more prone to serious side effects
- have kidney problems. Your doctor may give you a lower dose
- have a brain disease or a metabolic condition affecting your brain
- have a 'urea cycle disorder' where too much ammonia builds up in the body
- have an illness called 'systemic lupus erythematosus (SLE)' – a disease of the immune system which affects skin, bones, joints and internal organs
- know that there is a genetic problem caused by a mitochondrial disorder in your family. If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking EVALEX IV
- are having surgery, including dental surgery, tell the doctor or dentist that you are receiving EVALEX IV. You will need to take extra care in cleaning your teeth to prevent infection, as side effects of EVALEX IV include bleeding and swelling of the gums (see section 4).

*Liver damage*
EVALEX IV may cause severe and life-threatening damage to your liver. Signs that you may notice include seizures that are becoming more severe or happen more often, or excessive tiredness, lack of energy, weakness, stomach pain, loss of appetite, nausea, vomiting, yellow skin and eye whites or swelling of the face. Tell your doctor immediately if you notice these symptoms.
If your child is under 3 years of age, EVALEX IV should not be administered together with aspirin.

*Pancreas damage*
EVALEX IV may cause serious or life-threatening damage to the pancreas. This may occur at any time during your treatment. If you experience any of the following symptoms, tell your doctor immediately: stomach pain, nausea, vomiting, or loss of appetite.

*Suicidal thoughts and behaviour*
A small number of people being treated with antiepileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
There may also be a risk that you will experience changes in your mental health if your condition is not treated.

*Convulsions*
Convulsions may become worse or happen more frequently while taking this medicine. If this happens contact your doctor immediately.

*Weight gain*
Having EVALEX IV may make you put on weight. Talk to your doctor about how this will affect you.

*Blood tests*
Your doctor may wish to do blood tests before you are given EVALEX IV and during your treatment.

*Children and adolescents*
While treated with EVALEX IV, do not give salicylates (aspirin) to children under 3 years due to the risk of liver toxicity. Additionally, do not use salicylates in children under 16 years as it can increase the risk of Reye's syndrome (an acute condition that causes swelling in the brain and liver).

*Children (male and female) less than 18 years of age:*
EVALEX IV should be used with caution in male and female children under the age of 18 years, for the treatment of epilepsy.

For female children, ensure that the conditions of the pregnancy prevention programme are met.
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 "Possible side effects"). 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.

**Other medicines and EVALEX IV**

Always tell your healthcare provider if you are taking any other medicine. This includes complementary or traditional medicines.

*The following medicines can increase the chance of you getting side effects, when given with EVALEX IV:*
- some medicines used for pain and inflammation (salicylates) such as aspirin
- some other medicines used to treat fits – see section 3, 'Patients taking other medicines for fits (epilepsy)'. This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, lamotrigine and felbamate
- acetazolamide used to treat glaucoma, oedema or fits.

*EVALEX IV Injection may increase the effect of the following medicines:*
- medicines for depression, for example, monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline
- medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam, olanzapine and lithium
- propofol – used for anaesthesia
- zidovudine used to treat HIV infection
- nimodipine (used to decrease problems due to a certain type of bleeding in the brain)
- temozolomide used to treat cancer
- medicines used for thinning the blood (such as warfarin).

*The following medicines can affect the way EVALEX IV works:*
- some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- cimetidine used for stomach ulcers
- antibiotics e.g. erythromycin, carbapenems (antibiotics used to treat bacterial infections). The combination of valproic acid and carbapenems should be avoided because it may decrease the effect of sodium valproate
- rifampicin used to treat tuberculosis and other infections
- protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS
- cholestyramine used to lower blood fat (cholesterol) levels. It may still be possible for you to be given EVALEX IV; your doctor will advise you on what is suitable for you
- oestrogen-containing products (including some birth control pills)
- metamizole, a pain killer, may reduce the effect of EVALEX IV.

**Using EVALEX IV with food and drink**

Alcohol intake is not recommended during treatment.
You should not drink alcoholic drinks while you are treated with EVALEX IV.

**Pregnancy, breastfeeding and fertility**

**If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult with your doctor, pharmacist or other healthcare provider for advice before this medicine is administered to you.**

*Pregnancy*

**If you are pregnant, you should not be given EVALEX IV, unless other treatments are not effective or well tolerated. Do not stop receiving EVALEX IV without consulting your doctor as doing so could cause harm to you or an unborn child.**
If you are a woman able to have a baby, you must not receive EVALEX IV unless you use an effective method of birth control (contraception) during your entire treatment with EVALEX IV. Speak to your doctor if you have any questions about which contraceptive method is appropriate for you.
EVALEX IV can cause malformation and problems with early development of children if they are exposed to valproates in the womb.

EVALEX IV can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.

Hearing problems or deafness have been reported in children exposed to valproate during pregnancy.

It is estimated that up to 30 - 40 % of preschool children whose mothers took sodium valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. Autistic spectrum disorders are more often diagnosed in children exposed to valproate during pregnancy and there is some evidence that children exposed to sodium valproate during pregnancy are at increased risk of developing attention deficit hyperactivity disorder (ADHD).

Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking EVALEX IV. If you decide later, you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.

**Tell your doctor at once if you become pregnant, think you might be pregnant or are planning to become pregnant. Your doctor will urgently review your treatment.**
If you are a parent or a caregiver of a female child treated with valproate, as in EVALEX IV, you should contact their doctor once your child experiences their first period.

*Breastfeeding*
Sodium valproate, the active substance of EVALEX IV, gets into the breast milk. You should not breastfeed your baby if you are receiving EVALEX IV.

*Fertility*
EVALEX IV may decrease your fertility. It is unclear if this effect is reversible after discontinuation of EVALEX IV.
Male fertility: Using EVALEX IV can be a contributing factor in male infertility.

**Driving and using machines**

You may experience drowsiness when you are first given EVALEX IV, or if you are also taking other medicines, such as other antiepileptic medicines or benzodiazepines. If affected, you should not drive or operate machinery.
It is not always possible to predict to what extent EVALEX IV may interfere with your daily activities. You should ensure that you do not engage in driving or operating machinery until you are aware of the measure to which EVALEX IV affects you.

**EVALEX IV contains sodium**

Each 3 ml ampoule contains 44,5 mg sodium (cooking/table salt). This is equivalent to 2 % of the recommended maximum daily dietary intake of 2 g sodium for an adult.
Each 4 ml ampoule contains 59,2 mg sodium. This is equivalent to 3 % of the recommended maximum daily dietary intake of 2 g sodium for an adult.
Each 10 ml ampoule contains 148,2 mg sodium (cooking/table salt). This is equivalent to 7 % of the recommended maximum daily dietary intake of 2 g sodium for an adult.

**3. How EVALEX IV will be administered**

You will not be expected to give yourself EVALEX IV. It will be given to you by a person who is qualified to do so.
EVALEX IV treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

*Dosage*
Your doctor will decide on the amount of EVALEX IV you will be given. This will depend on your age and weight and will be adjusted to achieve adequate control of your seizures. If you have been taking sodium valproate by mouth, the dose given to you will be the same by injection. Your doctor will tell you when you are ready to switch over to an oral dosage form of valproate.
If you have been receiving other medicines for epilepsy the dose of EVALEX IV will be increased gradually over about 2 weeks. The total daily dose will normally be given by three or four slow injections, lasting 3-5 minutes, into your veins during the day, or by a continuous infusion (drip).

*Patients with kidney problems*
Your doctor may decide to adjust your or your child's dose.

*Patients taking other medicines for fits (epilepsy)*
You or your child may be taking other medicines for epilepsy at the same time as EVALEX IV. If so, your doctor should gradually initiate treatment depending on your or your child's condition.
If you have any concerns tell your doctor or nurse. It is important for you to keep having your EVALEX IV treatment until your doctor decides to stop. If you stop, your seizures may return.

*Tests*
Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. EVALEX IV can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly.

**If you receive more EVALEX IV than you should**

Since a healthcare provider will administer EVALEX IV, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

**If you miss a dose of EVALEX IV**

Since a healthcare provider will administer EVALEX IV, it is unlikely that the dose will be missed.

**4. Possible side effects**

EVALEX IV can have side effects.
Not all side effects reported for EVALEX IV are included in this leaflet. Should your general health worsen or if you experience any untoward effects while using EVALEX IV, please consult your doctor healthcare provider for advice.

**If any of the following happens, tell your doctor immediately:**

- You have an allergic reaction.
  The signs include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs (also known as DRESS syndrome).
- Liver problems and problems of the pancreas:
  A sudden illness which may happen in the first six months of treatment. It includes feeling and being sick many times; being very tired, sleepy and weak; stomach pain including very bad upper stomach pain; jaundice (yellowing of the skin or whites of the eyes); loss of appetite; swelling (especially of the legs and feet but may include other parts of the body); worsening of your fits or a general feeling of being unwell. It may sometimes even lead to death.

These are all very serious side effects. If you have them, you may have had a serious reaction to EVALEX IV. You may need urgent medical attention or further hospitalisation.

*Tell your doctor immediately if you notice any of the following:*
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'.
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also, flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'.
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also, a feeling of being generally unwell, fever, chills, and aching muscles. This may be something called 'Toxic epidermal necrolysis'.
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason.
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma).
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion).
- Changes in behaviour including being very alert, and sometimes also aggressive, hyperactive and unusual or inappropriate behaviour. This is more likely if other medicines to treat fits, such as phenobarbital and topiramate, are taken at the same time or if the starting dose of EVALEX IV is high or has been suddenly increased.
- An increase in the number and severity of convulsions.
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and coordination, feeling lethargic or less alert.
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements.
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits.

These are all serious side effects. You may need urgent medical attention.

**Tell your doctor if you notice any of the following:**

*Frequent side effects:*
- Anaemia (the number of red blood cells in your body is too low), causing weakness, fatigue, pale skin
- Too low blood sodium concentration (signs may be mental changes, headache, nausea, vomiting, tiredness, muscle spasms)
- Weight gain (see "Warnings and precautions")
- State of confusion, hallucinations (seeing and hearing things that do not exist)
- Aggression, agitation
- Attention disturbances
- Sleepiness
- Convulsions
- Trembling of hands and arms, clumsiness or unsteadiness
- Headache
- Involuntary eye movements (nystagmus)
- Dizziness
- Hearing loss (which may be irreversible)
- Diarrhoea
- Nausea, vomiting
- Indigestion
- Gum disease (swollen gums)
- Stomach or abdominal pain.
- Sore mouth
- Hair loss or thinning of hair
- Nail and nail bed disorders
- Losing bladder control (incontinence)
- Painful menstrual periods.

*Less frequent side effects*
- Hyperandrogenism (excessive presence of male hormones in females including symptoms like excessive hair growth, acne, male pattern hair loss)
- Double vision (diplopia)
- Encephalopathy (an altered mental state – declining ability to reason and concentrate, memory loss, personality change, seizures and twitching may be experienced)
- Lethargy (a lack of energy)
- Parkinsonism (which is reversible), lack of muscle control, affected movement, speech (ataxia)
- Pins and needles sensation in arms, hands, legs and feet (paraesthesia)
- Dementia (which is reversible)
- Trouble understanding things (cognitive disorder)
- Sedation
- Vasculitis (inflammation of the blood vessels – you may experience fever, fatigue, weight loss and muscle and joint pain)
- Build-up of fluid in the area between the layers of tissue that line the lungs causing chest pain, cough, difficulty breathing
- Skin rash
- Change in hair texture, colour, growth
- Decreased bone mineral density (brittle bones and fractures)
- Osteoporosis (brittle bones), osteopenia (reduced bone mass)
- Frequent urination at night
- Inflammation of the kidneys (back pain, fever)
- Fanconi syndrome: a rare disorder of kidney tubule function that causes increased urination, increased thirst, pain and weakness in muscle and bones
- Absent menstrual periods or abnormal bleeding from uterus
- Male infertility
- Polycystic ovaries (symptoms may be weight gain, irregular periods, heavy bleeding)
- Swollen breasts in males
- Feeling very cold, shivering (hypothermia)
- Swelling of the hands, ankles and feet
- Myelodysplastic syndrome (symptoms may include fatigue, shortness of breath and unusual paleness). This is a condition where immature blood cells in the bone marrow do not mature and therefore do not become healthy blood cells.

*Frequency unknown*
- Malformation of the foetus and developmental disorders (see "Pregnancy, breastfeeding and fertility" and "Warnings and precautions").

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

*Reporting of side effects*
If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects 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.
By reporting side effects, you can help provide more information on the safety of EVALEX IV.

**5. How EVALEX IV will be stored**

Store all medicines out of reach of children.
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.
Do not use EVALEX IV after the expiry date printed on the label or carton.
Return any expired or unused medicine to your pharmacist for safe disposal. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

**6. Content of the pack and other information**

**What EVALEX IV contains:**

- The active substance is sodium valproate 100 mg per 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.
- The other ingredients are potassium dihydrogen phosphate (buffer), disodium phosphate dodecahydrate (buffer) and water for injections.

**What EVALEX IV looks like and contents of the pack**

EVALEX IV solution for injection or infusion is a clear colourless solution, free from visible particles.
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: 10 ml of solution is packed in a 10 ml capacity ampoule.
Not all pack sizes and strengths may be marketed at one time.

**Holder of the Certificate of Registration**
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**This leaflet was last revised in**
Registration date: 11 July 2023

**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

**PASIËNTINLIGTINGSBLAD**

**Valproaat, soos in EVALEX™ IV, kan geboortedefekte en vroeë ontwikkelingsprobleme veroorsaak indien dit tydens swangerskap toegedien word. Indien jy 'n vrou is wat swanger kan raak, moet jy vir die duur van jou behandeling effektiewe voorbehoeding gebruik (kyk "Swangerskap, borsvoeding en vrugbaarheid"). Lig jou dokter dadelik in as jy wil swanger raak, of dink jy is dalk swanger. Indien jy die ouer of versorger is van 'n vroulike kind wat met EVALEX IV behandel word, lees die afdeling in hierdie inligtingsblad oor Swangerskap en borsvoeding sorgvuldig.**

**SKEDULERINGSTATUS: S3**

**EVALEX™ 300 mg IV**
**EVALEX™ 400 mg IV**
**EVALEX™ 1 g IV**

Oplossing vir inspuiting of infusie (100 mg/ml)
Natriumvalproaat
Suikervry
Bevat natrium:
44,5 mg/3 ml; 59,2 mg/4 ml and 148,2 mg/10 ml

**Lees die hele inligtingsblad aandagtig deur voordat EVALEX IV aan jou gegee word**
- Hou hierdie inligtingsblad. Dit mag nodig wees dat jy dit weer wil lees.
- Indien jy nog vrae het, vra jou dokter, apteker, verpleegster of ander gesondheidsorgverskaffer.

**Wat is in hierdie inligtingsblad**

1. Wat is EVALEX IV en waarvoor word dit gebruik
2. Wat jy moet weet voordat EVALEX IV aan jou gegee word
3. Hoe EVALEX IV toegedien sal word
4. Moontlike newe-effekte
5. Hoe EVALEX IV bewaar sal word
6. Inhoud van die pakkie en ander inligting

**1. Wat is EVALEX IV en waarvoor word dit gebruik**

EVALEX IV bevat natriumvalproaat, wat behoort tot 'n groep medisyne genaamd anti-epileptika. Hierdie middels word gebruik om epileptiese aanvalle te beheer. EVALEX IV oplossing vir inspuiting word gebruik om verskeie tipes epileptiese aanvalle (toevalle) te behandel wanneer natriumvalproaat-tablette nie geneem kan word nie.
EVALEX IV word ook vir manie gebruik: jy kan dalk opgewonde, uitbundig, rusteloos, entoesiasties of hiperaktief voel. Manie kom voor by 'n siekte genaamd "bipolêre versteuring".

**2. Wat jy moet weet voordat EVALEX IV aan jou gegee word**

**EVALEX IV moet nie aan jou toegedien word nie:**
- indien jy hipersensitief (allergies) is vir natriumvalproaat of enige van die bestanddele van EVALEX IV (gelys in Afdeling 6)
- indien jy lewerprobleme het, of 'n familiegeskiedenis van lewerprobleme
- indien jy aan porfirie ly ('n seldsame toestand wat die afbraak van komponente van rooibloedselle beïnvloed)
- indien jy 'n genetiese probleem het wat 'n mitochondriale versteuring veroorsaak (bv. Alpers-Huttenlocher-sindroom)
- indien jy aan ureumsiklusversteuring ('n tipe metaboliese versteuring) ly
- indien jy swanger is, of jou baba borsvoed. Kyk "Waarskuwings en voorsorgmaatreëls" en "Swangerskap, borsvoeding en vrugbaarheid".

**Waarskuwings en voorsorgmaatreëls**

*Praat met jou dokter of gesondheidsorgverskaffer voordat jy EVALEX IV ontvang, indien jy:*
- diabetes het. EVALEX IV kan die resultate van urientoetse beïnvloed
- 'n karnitien-palmitoïeltransferase tipe II-tekort het, wat verhoed dat die liggaam sekere vette vir energie gebruik, aangesien jy meer geneig kan wees tot ernstige newe-effekte
- nierprobleme het. Jou dokter kan moontlik 'n laer dosis vir jou voorskryf
- 'n breinsiekte het of 'n metaboliese siektetoestand wat jou brein aantas
- 'n 'ureumsiklusversteuring' het, waarby te veel ammoniak in die liggaam opbou
- 'n siekte genaamd 'sistemiese lupus eritematose' (SLE) het - 'n siekte van die immuunstelsel wat die vel, bene, gewrigte en inwendige organe aantas
- weet dat daar 'n genetiese probleem is wat veroorsaak word deur 'n mitochondriale versteuring in jou familie. Indien jy nie seker is of enige van die bogenoemde op jou van toepassing is nie, praat met jou dokter of apteker voordat jy EVALEX IV ontvang
- 'n operasie ondergaan, insluitend tandheelkundige chirurgie, lig die dokter of tandarts in dat jy EVALEX IV ontvang. Jy moet ekstra sorg neem om jou tande skoon te borsel om infeksie te voorkom, aangesien newe-effekte van EVALEX IV bloeding en swelling van die tandvleis insluit (kyk afdeling 4).

*Lewerskade*
EVALEX IV kan ernstige en lewensgevaarlike skade aan jou lewer veroorsaak. Tekens wat jy dalk kan opmerk, sluit in aanvalle wat ernstiger word of meer gereeld voorkom, of uitermatige moegheid, gebrek aan energie, swakheid, maagpyn, verlies van eetlus, naarheid, braking, geel vel en oogwitte of swelling van die gesig. Lig dadelik jou dokter in as jy enige van hierdie simptome waarneem.
As u kind jonger as 3 jaar is, moet EVALEX IV nie saam met aspirien toegedien word nie.

*Skade aan die pankreas*
EVALEX IV kan ernstige of lewensgevaarlike skade aan die pankreas veroorsaak. Dit kan enige tyd tydens jou behandeling voorkom. Indien jy enige van die volgende simptome ervaar, lig jou dokter dadelik in: maagpyn, naarheid, braking of verlies van eetlus.

*Selfdood-gedagtes en -gedrag*
'n Klein groepie mense wat met anti-epileptika soos natriumvalproaat behandel word, het gedagtes aan self-besering of selfdood gehad. Indien jy op enige tydstip sulke gedagtes koester, moet jy dadelik jou dokter kontak.
Daar kan ook 'n risiko wees dat jy veranderinge in jou geestesgesondheid sal ervaar as jou siektetoestand nie behandel word nie.

*Stuiptrekkings*
Stuiptrekkings kan erger word of meer dikwels voorkom terwyl hierdie medisyne gebruik word. Indien dit gebeur kontak dadelik jou dokter.

*Gewigstoename*
Gebruik van EVALEX IV kan jou laat gewig aansit. Gesels met jou dokter oor hoe dit jou sal beïnvloed.

*Bloedtoetse*
Jou dokter sal dalk bloedtoetse wil doen voordat EVALEX IV aan jou gegee word en tydens jou behandeling.

*Kinders en adolessente*
Gedurende behandeling met EVALEX IV moet kinders onder 3 jaar nie salisilate (aspirien) gegee word nie, weens die risiko van lewertoksisiteit. Daarbenewens moet jy nie salisilate by kinders jonger as 16 jaar gebruik nie, aangesien dit die risiko van Reye-sindroom ('n akute toestand wat swelling in die brein en lewer veroorsaak) kan verhoog.

*Kinders (manlik en vroulik) onder 18 jarige ouderdom:*
EVALEX IV moet met omsigtigheid gebruik word vir die behandeling van epilepsie by manlike en vroulike kinders jonger as 18 jaar.

Maak seker dat die voorwaardes van die swangerskapsvoorkomingsprogram nagekom word vir vroulike kinders.
Sommige psigiatriese versteurings, insluitend aggressie, agitasie, aandagversteuring, abnormale gedrag, psigomotoriese hiperaktiwiteit en leerprobleme kan by pediatriese pasiënte wat EVALEX IV ontvang waargeneem word (kyk "Moontlike newe-effekte"). Daar is tans geen afdoende bewyse rakende die moontlikheid van skade aan die voortplantingstelsel, skeletstelselgroei of breinontwikkeling by pasiënte onder die ouderdom van 18 jaar nie.

**Ander medisyne en EVALEX IV**

Lig altyd jou gesondheidsorgverskaffer in as jy enige ander medisyne neem. Dit sluit komplementêre of tradisionele medisyne in.

*Die volgende medisyne kan die kans verhoog dat jy newe-effekte kry wanneer dit saam met EVALEX IV gegee word:*
- sommige medisyne wat gebruik word vir pyn en inflammasie (salisilate) soos aspirien
- sommige ander medisyne wat gebruik word om aanvalle te behandel – kyk afdeling 3, 'Pasiënte wat ander medisyne vir aanvalle (epilepsie) neem'. Dit sluit medisyne in soos fenobarbitaal, primidoon, fenitoïen, karbamasepien, rufinamied, topiramaat, lamotrigien en felbamaat
- asetasoolamied gebruik vir die behandeling van gloukoom, edeem of toevalle.

*EVALEX IV inspuiting kan die effek van die volgende medisyne versterk:*
- medisyne vir depressie, byvoorbeeld monoamienoksidase-inhibeerders (MAOI) soos moklobemied, selegilien
- medisyne wat gebruik word om emosionele en geestesgesondheidsprobleme te verlig (insluitend skisofrenie, bipolêre versteuring en depressie) soos kwetiapien, diasepaam, olansapien en litium
- propofol - gebruik vir narkose
- sidovudien - gebruik vir die behandeling van MIV-infeksie
- nimodipien (gebruik om probleme as gevolg van 'n sekere tipe bloeding in die brein te verminder)
- temosolomied gebruik vir die behandeling van kanker
- medisyne gebruik om die bloed te verdun (soos warfarien).

*Die volgende medisyne kan die manier waarop EVALEX IV werk beïnvloed:*
- sommige medisyne wat gebruik word vir die voorkoming en behandeling van malaria, soos meflokien en chlorokien
- simetidien, gebruik vir maagsere
- antibiotika bv. eritromisien, karbapeneme (antibiotika gebruik vir die behandeling van bakteriële infeksies). Die kombinasie van valproïensuur en karbapeneme moet vermy word omdat dit die effek van natriumvalproaat kan verminder
- rifampisien, gebruik vir die behandeling van tuberkulose en ander infeksies
- proteaseremmers soos lopinavir en ritonavir - gebruik vir MIV-infeksie en VIGS
- cholestiramien, gebruik om bloedvetvlakke (cholesterol) te verlaag. Jy kan egter steeds EVALEX IV kry; jou dokter sal jou raad gee oor wat geskik is vir jou
- estrogeen-bevattende produkte (insluitend sommige voorbehoedpille)
- metamisool, 'n pynstiller, wat die effek van EVALEX IV kan verminder.

**Gebruik van EVALEX IV met kos en vloeistowwe**

Die inname van alkohol tydens die behandeling word nie aanbeveel nie.
Jy moet nie alkoholiese drankies neem terwyl jy met EVALEX IV behandel word nie.

**Swangerskap, borsvoeding en vrugbaarheid**

**Indien jy swanger is of borsvoed, dink jy is dalk swanger, of beplan om 'n baba te hê, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer voordat hierdie medisyne aan jou toegedien word.**

*Swangerskap*

**As jy swanger is moet EVALEX IV nie aan jou gegee word nie, tensy ander behandelings nie effektief is of goed verdra word nie. Moenie ophou om EVALEX IV te ontvang sonder om jou dokter te raadpleeg nie, aangesien dit skade aan jou of 'n ongebore kind kan veroorsaak.**
As jy 'n vrou is wat 'n baba kan hê, moet jy nie EVALEX IV ontvang nie, tensy jy 'n effektiewe metode van voorbehoeding (kontrasepsie) tydens jou behandeling met EVALEX IV gebruik. Praat met jou dokter as jy enige vrae het oor watter voorbehoedmetode geskik is vir jou.
EVALEX IV kan wanvorming en vroeë ontwikkelingsprobleme by kinders wat in die baarmoeder aan valproaat blootgestel word veroorsaak.

EVALEX IV kan ernstige geboortedefekte veroorsaak en kan die ontwikkeling van die kind tydens die groeiproses beïnvloed. Geboortedefekte wat aangemeld is, sluit in spina bifida (waar die bene van die ruggraat nie behoorlik ontwikkel is nie); gesig- en skedelmisvormings; misvormings van die hart, niere, urienweg en geslagsdele; gebreklike ledemate.
Gehoorprobleme of doofheid is aangemeld by kinders wat tydens swangerskap aan valproaat blootgestel is.

Daar word beraam dat tot 30 - 40 % van voorskoolse kinders wie se moeders natriumvalproaat tydens swangerskap geneem het, probleme met vroeë kinderontwikkeling kan hê. Kinders wat geaffekteer word kan stadiger loop en praat, is intellektueel tot minder in staat as ander kinders, en sukkel met taal en geheue. Outistiese spektrum afwykings word meer gereeld gediagnoseer by kinders wat tydens swangerskap aan valproaat blootgestel was, en daar is bewyse dat kinders wat tydens swangerskap aan natriumvalproaat blootgestel was, 'n groter risiko het om aandaggebrek-hiperaktiwiteitsteuring (AGHS) te ontwikkel.

Voordat hierdie medisyne aan jou voorgeskryf word, sou jou dokter verduidelik het wat met jou baba kan gebeur as jy swanger word terwyl jy EVALEX IV ontvang. Indien jy later besluit om 'n kind te hê, moet jy nie ophou om jou medisyne of metode van geboortebeperking (kontrasepsie) te gebruik voordat jy dit met jou dokter bespreek het nie.

**Lig jou dokter dadelik in as jy swanger is, dink jy is dalk swanger, of as jy beplan om swanger te raak. Jou dokter sal jou behandeling dringend wil hersien.**
Indien jy 'n ouer of 'n versorger is van 'n vroulike kind wat met valproaat soos in EVALEX IV behandel word, moet jy hul dokter kontak sodra jou kind hul eerste maandstonde ervaar.

*Borsvoeding*
Natriumvalproaat, die aktiewe bestanddeel van EVALEX IV, kom voor in borsmelk. Indien jy EVALEX IV ontvang moet jy nie jou baba borsvoed nie.

*Vrugbaarheid*
EVALEX IV kan jou vrugbaarheid verminder. Dit is onduidelik of hierdie effek omkeerbaar is na staking van EVALEX IV.
Manlike fertiliteit: Die gebruik van EVALEX IV kan 'n bydraende faktor wees by manlike onvrugbaarheid.

**Bestuur en die gebruik van masjinerie**

Jy kan lomerigheid ervaar wanneer jy die eerste keer EVALEX IV gegee word, of as jy ook ander medisyne gebruik, soos ander anti-epileptiese medisyne of bensodiasepiene. Indien dit gebeur moet jy nie bestuur of masjiene hanteer nie.
Dit is nie altyd moontlik om te voorspel tot hoe 'n mate EVALEX IV jou daaglikse aktiwiteite kan beïnvloed nie. Jy moet sorg dat jy nie bestuur of masjinerie gebruik voordat jy nie weet tot hoe 'n mate EVALEX IV jou beïnvloed nie.

**EVALEX IV bevat natrium**

Elke 3 ml ampule bevat 44,5 mg natrium (kombuis/tafelsout). Dit is gelykstaande aan 2 % van die aanbevole maksimum daaglikse dieetinname van 2 g natrium vir 'n volwassene.
Elke 4 ml ampule bevat 59,2 mg natrium. Dit is gelykstaande aan 3 % van die aanbevole maksimum daaglikse dieetinname van 2 g natrium vir 'n volwassene.
Elke 10 ml ampule bevat 148,2 mg natrium (kombuis/tafelsout). Dit is gelykstaande aan 7 % van die aanbevole maksimum daaglikse dieetinname van 2 g natrium vir 'n volwassene.

**3. Hoe EVALEX IV toegedien sal word**

Daar sal nie van jou verwag word om EVALEX IV aan jouself toe te dien nie. Dit sal aan jou gegee word deur 'n persoon wat gekwalifiseer is om dit te doen.
Behandeling met EVALEX IV moet begin en gemonitor word deur 'n dokter wat in die behandeling van epilepsie spesialiseer.

*Dosis*
Jou dokter sal besluit hoeveel EVALEX IV aan jou gegee moet word. Dit sal afhang van jou ouderdom en gewig en sal aangepas word om voldoende beheer oor jou aanvalle te verkry. Indien jy natriumvalproaat per mond geneem het, sal die dosis wat aan jou gegee word dieselfde wees met 'n inspuiting. Jou dokter sal jou inlig wanneer jy gereed is om oor te skakel na 'n mondelike doseervorm van valproaat.
Indien jy ander medisyne vir epilepsie ontvang het, sal die dosis EVALEX IV geleidelik oor ongeveer 2 weke verhoog word. Die totale daaglikse dosis word gewoonlik deur drie of vier stadige 3-5 minute inspuitings gedurende die dag in jou are of deur 'n deurlopende infusie (drup) toegedien.

*Pasiënte met nierprobleme*
Jou dokter kan besluit om jou of jou kind se dosis aan te pas.

*Pasiënte wat ander medisyne neem vir toevalle (epilepsie)*
Jy of jou kind kan dalk ander medisyne vir epilepsie gelyktydig met EVALEX IV neem. Indien dit die geval is sal jou dokter die behandeling geleidelik begin, afhangende van jou of jou kind se siektetoestand.
Indien jy oor iets bekommerd is, lig jou dokter of verpleegster in. Dit is belangrik dat jy aanhou om jou EVALEX IV-behandeling te kry totdat jou dokter besluit om dit te staak. Indien jy ophou daarmee, kan jou aanvalle terugkeer.

*Toetse*
Maak seker dat jy of jou kind julle gereelde opvolgafsprake nakom. Hulle is baie belangrik aangesien jou of jou kind se dosis dalk verander moet word. EVALEX IV kan die vlakke van lewerensieme wat deur bloedtoetse aangetoon word, verander. Dit kan beteken dat jou of jou kind se lewer nie behoorlik werk nie.

**Indien jy meer EVALEX IV ontvang as wat jy moes**

Aangesien 'n gesondheidsorgverskaffer EVALEX IV sal toedien, sal hy/sy die dosis beheer. In die geval van oordosis sal jou dokter egter die oordosis behandel.

**Indien jy 'n dosis EVALEX IV oorgeslaan het:**

Aangesien 'n gesondheidsorgverskaffer EVALEX IV sal toedien, is dit onwaarskynlik dat 'n dosis oorgeslaan sal word.

**4. Moontlike newe-effekte**

EVALEX IV kan newe-effekte hê.
Nie alle newe-effekte wat vir EVALEX IV aangemeld is, is by hierdie inligtingsblad ingesluit nie. Indien jou algemene gesondheid agteruitgaan of jy enige ongunstige effekte ervaar terwyl jy EVALEX IV ontvang, raadpleeg asseblief jou gesondheidsorgverskaffer.

**Lig dadelik jou dokter in, indien:**

- Jy 'n allergiese reaksie gehad het.
  Die tekens sluit in: 'n uitslag, gewrigspyn, koors (sistemiese lupus eritematose), sluk- of asemhalingsprobleme, swelling van jou lippe, gesig, keel of tong. Hande, voete of geslagsdele kan ook aangetas word. Erger allergiese reaksies kan lei tot vergrote limfkliere en moontlike belemmering van ander organe (ook bekend as DRESS-sindroom).
- Jy lewerprobleme en probleme met die pankreas het:
  'n Skielike siekte wat in die eerste ses maande van behandeling kan voorkom. Dit sluit in: voel naar en bring dikwels op; voel baie moeg, slaperig en swak; maagpyn insluitend baie erge bobuikpyn; geelsug (vergeling van die vel of witte van die oë); verloor eetlus; swelling (veral van die bene en voete, maar dit kan ander dele van die liggaam insluit); verergering van jou toevalle of 'n algemene gevoel van ongesteldheid. Dit kan somtyds selfs tot die dood lei.

Al hierdie newe-effekte is baie ernstig. Indien jy dit ervaar, kan jy moontlik 'n ernstige reaksie op EVALEX IV hê. Jy kan dringende mediese aandag of verdere hospitalisering benodig.

*Lig jou dokter dadelik in as jy enige van die volgende waarneem:*
- 'n Uitslag of velletsels met 'n pienk/rooi ring en 'n ligte middelpunt wat dalk jeukerig, skilferig of vol vloeistof kan wees. Die uitslag kan veral op die handpalms of voetsole verskyn. Dit kan tekens wees van 'n ernstige allergie vir die medisyne genaamd 'erythema multiforme'.
- Blaarvorming of bloeding van die vel rondom die lippe, oë, mond, neus en geslagsorgane. Ook, griepagtige simptome en koors. Dit kan 'n verskynsel wees wat bekend staan as 'Steven-Johnson-sindroom'.
- Erge blaserige uitslag wat lae van die vel kan laat afdop om groot dele rou vel oor die liggaam te ontbloot. Ook algemene ongesteldheid, koors, kouekoors en seer spiere. Dit kan iets wees wat bekend staan as 'Toksiese epidermale nekrolise'.
- Jy makliker kneus en meer infeksies as gewoonlik kry. Dit kan 'n bloedprobleem wees wat bekend staan as 'trombositopenie'. Dit kan ook wees te wyte aan 'n afname in die aantal witbloedselle, beenmurgonderdrukking of 'n ander toestand wat rooibloedselle, witbloedselle en bloedplaatjies (pansitopenie), of bloedstolling beïnvloed.
- Bloedstollingsprobleme (bloeding vir langer as normaal), kneusing of bloeding sonder rede.
- Gemoedswisselings, geheueverlies, swak konsentrasie en diepgaande verlies van bewussyn (koma).
- Onderaktiewe skildklier, wat moegheid of gewigstoename (hipotireose) kan veroorsaak.
- Asemhalingsprobleme en pyn weens inflammasie van die longe (pleurale effusie).
- Veranderinge in gedrag, insluitend om baie op-en-wakker te wees en soms ook aggressief, hiperaktief en toon ongewone of onvanpaste gedrag. Dit is meer waarskynlik wanneer ander medisyne wat gebruik word om aanvalle te behandel, soos fenobarbitaal en topiramaat, gelyktydig geneem word, of as die aanvangsdosis van EVALEX IV hoog is, of skielik verhoog word.
- 'n Toename in die aantal en erns van konvulsies.
- Verandering in die hoeveelheid ammoniak in die bloed. Simptome van hierdie toestand sluit in braking, probleme met balans en koördinasie, lusteloosheid of gebrek aan waaksaamheid.
- Bewerig voel (bewing), slaperig of onstabiel voel wanneer jy loop, of rukkerige spierbewegings.
- Voel moeg of verward met verlies van bewussyn, soms gepaardgaande met hallusinasies of stuipe.

Hierdie is almal ernstige newe-effekte. Jy kan dringende mediese aandag benodig.

**Lig jou dokter in as jy enige van die volgende waarneem:**

*Gereelde newe-effekte:*
- Anemie (die aantal rooibloedselle in jou liggaam is te min), veroorsaak swakheid, moegheid, bleek vel
- Te lae natriumvlakke in die bloed (tekens kan verandering in geestestoestand, hoofpyn, naarheid, braking, moegheid, spierkrampe insluit)
- Gewigstoename (kyk "Waarskuwings en voorsorgmaatreëls")
- Verwarde toestand, hallusinasies (sien en hoor dinge wat nie bestaan nie)
- Aggressie, rusteloosheid
- Aandagversteuring
- Lomerigheid
- Konvulsies
- Bewing van hande of arms, lompheid of onvastheid
- Hoofpyn
- Onwillekeurige oogbewegings (nistagmus)
- Duiseligheid
- Gehoorverlies (wat omkeerbaar kan wees)
- Diarree
- Naarheid, braking
- Swak spysvertering
- Tandvleis aandoening (geswelde tandvleis)
- Maag- of buikpyn
- Seer mond
- Haarverlies en hare word dunner
- Nael- en naelbedversteurings
- Verloor van blaasbeheer (inkontinensie)
- Pynlike maandstondes

*Minder algemene newe-effekte*
- Hiperandrogenisme (oormaat manlike hormone by vroue, insluitend simptome soos oortollige haargroei, aknee, haarverlies volgens manlike patroon)
- Dubbelvisie (diplopie)
- Ensefalopatie ('n veranderde geestestoestand - afnemende vermoë om te redeneer en te konsentreer, geheueverlies, persoonlikheidsverandering, aanvalle en spiertrekkings kan ervaar word)
- Letargie (lusteloosheid)
- Parkinsonisme (wat omkeerbaar is), gebrek aan spierbeheer, beperkte beweging, spraak (ataksie)
- Gevoel van speld-en-naaldprikkels in die arms, hande, bene en voete (parestesie)
- Demensie (wat omkeerbaar is)
- Sukkel om dinge te verstaan (kognitiewe versteuring)
- Kalmering
- Vaskulitis (ontsteking van die bloedvate – jy kan koors, moegheid, gewigsverlies en spier- en gewrigspyn ervaar)
- Ophoping van vloeistof in die area tussen die weefsellae wat die longe uitvoer, wat borspyn, hoes en moeilike asemhaling veroorsaak
- Veluitslag
- Verandering in haartekstuur, kleur en groei
- Verminderde beenmineraaldigtheid (bros bene en frakture)
- Osteoporose (bros bene), osteopenie (verminderde beenmassa)
- Gereelde urinering saans
- Inflammasie van die niere (rugpyn, koors)
- Fanconi-sindroom: 'n seldsame disfunksie van die nierbuisies wat verhoogde urinering, verhoogde dors, pyn en swakheid in spiere en bene veroorsaak
- Afwesige maandstondes of abnormale bloeding uit uterus
- Manlike onvrugbaarheid
- Polisistiese eierstokke (simptome kan gewigstoename, onreëlmatige maandstondes, swaar bloeding insluit)
- Geswelde borste by mans
- Voel baie koud, bibber (hipotermie)
- Swelling van die hande, enkels en voete
- Miëlodisplastiese sindroom (simptome kan insluit moegheid, kortasemigheid en ongewone bleekheid). Dit is 'n toestand waar onvolwasse bloedselle nie in die beenmurg volwasse word nie en dus nie tot gesonde bloedselle ontwikkel nie.

*Frekwensie onbekend*
- Fetale misvormings en ontwikkelingsafwykings (kyk "Swangerskap, borsvoeding en vrugbaarheid" en "Waarskuwings en voorsorgmaatreëls").

Indien jy enige newe-effekte ondervind wat nie in hierdie inligtingsblad genoem word nie, lig asseblief jou dokter of apteker in.

*Aanmelding van newe-effekte*
Indien jy newe-effekte ondervind, bespreek dit met jou dokter, apteker of verpleegster. Jy kan ook newe-effekte by SAHPRA aanmeld deur middel van die "Adverse drug reactions & quality problem reporting form" wat aanlyn onder SAHPRA se publikasies beskikbaar is: https://www.sahpra.org.za/Publications/Index/8.
Deur newe-effekte aan te meld, kan jy help om meer inligting rakende die veiligheid van EVALEX IV te verskaf.

**5. Hoe EVALEX IV bewaar sal word**

Bewaar alle medisyne buite bereik van kinders.
Bewaar by of benede 25 °C. Hou die ampules in die oorspronklike verpakking totdat dit benodig word.
Die inhoud van die ampules is slegs vir enkelgebruik.
Moenie EVALEX IV na die vervaldatum wat op die etiket of karton aangedui is, gebruik nie.
Neem alle vervalde of ongebruikte medisyne terug na jou apteker om veilig daarvan ontslae te raak. Moenie ongebruikte medisyne in afvoerpype of rioolstelsels (bv. toilette) weggooi nie.

**6. Inhoud van die pakkie en ander inligting**

**Wat EVALEX IV bevat:**

- Die aktiewe bestanddeel is natriumvalproaat 100 mg per ml.
  Elke 3 ml ampule bevat 300 mg natriumvalproaat.
  Elke 4 ml ampule bevat 400 mg natriumvalproaat.
  Elke 10 ml ampule bevat 1 000 mg natriumvalproaat.
- Die ander bestanddele is kaliumdiwaterstoffosfaat (buffer), dinatriumfosfaatdodekahidraat (buffer) en water vir inspuiting.

**Hoe EVALEX IV lyk en inhoud van die pakkie**

EVALEX IV oplossing vir inspuiting of infusie is 'n helder kleurlose oplossing, vry van sigbare deeltjies.
Die helder oplossing vir inspuiting of infusie word verpak in tipe I deursigtige glas ampules in 'n kartonboksie wat 1, 4, 5 of 10 ampules bevat.

EVALEX 300 mg IV: 3 ml oplossing word verpak in 'n 5 ml ampule.
EVALEX 400 mg IV: 4 ml oplossing word verpak in 'n 5 ml ampule.
EVALEX 1 g IV: 10 ml oplossing word verpak in 'n 10 ml ampule.
Nie alle verpakkingsgroottes en sterktes word noodwendig bemark nie.

**Houer van die Registrasiesertifikaat**
**Macleods Pharmaceuticals SA (Edms) Bpk**
Kantoorblok 1, Bassonia Estate Kantoorpark (Oos),
Cussoniarylaan 1, Bassonia Rock, Uitbr.12, Alberton.
Tel: +27 11 682 1169

**Hierdie inligtingsblad is voorheen hersien in**
Registrasiedatum: 11 Julie 2023

**Registrasienommers**
EVALEX 300 mg IV: 53/2.5/0667
EVALEX 400 mg IV: 53/2.5/0668
EVALEX 1 g IV: 53/2.5/0669

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