PATIENT INFORMATION LEAFLET

Valproate, as in EXPALEX 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 EXPALEX IV, read the section on Pregnancy and breastfeeding in this leaflet carefully.

SCHEDULING STATUS: S3

EXPALEX™ 300 mg IV

EXPALEX™ 400 mg IV

EXPALEX™ 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 EXPALEX 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 EXPALEX IV is and what it is used for

EXPALEX IV contains sodium valproate, which belongs to a group of medicines called antiepileptics. These are used to control epileptic seizures. EXPALEX IV solution for injection is used to treat various types of epileptic seizures (fits) when it is not possible to take sodium valproate tablets.

EXPALEX 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 EXPALEX IV

EXPALEX IV should not be administered to you:

- if you are hypersensitive (allergic) to sodium valproate or any of the ingredients of EXPALEX 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 EXPALEX IV, if you:

- have diabetes. EXPALEX 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 EXPALEX IV
- are having surgery, including dental surgery, tell the doctor or dentist that you are receiving EXPALEX IV. You will need to take extra care in cleaning your teeth to prevent infection, as side effects of EXPALEX IV include bleeding and swelling of the gums (see section 4).

Liver damage

EXPALEX 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, EXPALEX IV should not be administered together with aspirin.

Pancreas damage

EXPALEX 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 EXPALEX 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 EXPALEX IV and during your treatment.

Children and adolescents

While treated with EXPALEX 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:

EXPALEX 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 EXPALEX 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 EXPALEX 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 EXPALEX 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.

EXPALEX 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 EXPALEX 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 EXPALEX 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 EXPALEX IV.

Using EXPALEX IV with food and drink

Alcohol intake is not recommended during treatment.

You should not drink alcoholic drinks while you are treated with EXPALEX 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 EXPALEX IV, unless other treatments are not effective or well tolerated.

Do not stop receiving EXPALEX 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 EXPALEX IV unless you use an effective method of birth control (contraception) during your entire treatment with EXPALEX IV. Speak to your doctor if you have any questions about which contraceptive method is appropriate for you.

EXPALEX IV can cause malformation and problems with early development of children if they are exposed to valproates in the womb.

EXPALEX 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 EXPALEX 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 EXPALEX IV, you should contact their doctor once your child experiences their first period.

Breastfeeding

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

Fertility

EXPALEX IV may decrease your fertility. It is unclear if this effect is reversible after discontinuation of EXPALEX IV.

Male fertility: Using EXPALEX IV can be a contributing factor in male infertility.

Driving and using machines

You may experience drowsiness when you are first given EXPALEX 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 EXPALEX 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 EXPALEX IV affects you.

EXPALEX 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 EXPALEX IV wil be administered

You will not be expected to give yourself EXPALEX IV. It will be given to you by a person who is qualified to do so.

EXPALEX 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 EXPALEX 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 EXPALEX 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 EXPALEX 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 EXPALEX 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. EXPALEX 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 EXPALEX IV than you should

Since a healthcare provider will administer EXPALEX 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 EXPALEX IV

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

4. Possible side effects

EXPALEX IV can have side effects.

Not all side effects reported for EXPALEX IV are included in this leaflet. Should your general health worsen or if you experience any untoward effects while using EXPALEX 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 EXPALEX 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 EXPALEX 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 EXPALEX IV can help provide more information on the safety of this medicine.

5. How EXPALEX 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 EXPALEX IV after the expiry date printed on the label, container or blister.

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 EXPALEX 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 EXPALEX IV looks like and contents of the pack

EXPALEX 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.

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

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

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

Not all pack sizes may be marketed at one time.

Holder of the Certificate of Registration

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