PACKAGE LEAFLET: INFORMATION FOR THE USER

Depakine® 400 mg/4 ml

preparation for IV injection

sodium valproate

sanofi

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.

WARNING

DEPAKINE CAN SERIOUSLY HARM AN UNBORN CHILD WHEN TAKEN DURING PREGNANCY.
Children exposed to valproate *in utero* have a high risk of serious developmental disorders (intellectual and motor) and behavioural disturbances (up to 30 to 40% of cases) and/or birth defects (approximately 11% of cases).
If you are a female child, a female adolescent, a woman of childbearing age:
- **your doctor will only prescribe valproate for you if other treatments are not effective or not tolerated.**
- **if no other treatment is possible, valproate will be prescribed for you and dispensed under the very strict conditions of a Pregnancy Prevention Program, which aims to prevent any pregnancy.**

If valproate has been prescribed for you and you are a woman childbearing age, you must, in particular:
- **use at least 1 effective method of contraception without interruptions during your entire treatment with Depakine. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.**
- **schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.**
- **do not stop taking Depakine unless your doctor tells you to as your condition may become worse.**

Make sure that you have read and understood the Patient Guide and signed the annual Risk Acknowledgment Form given to you by your specialist doctor experienced in the treatment of epilepsy.

Ask your doctor or pharmacist for advice.

If you are a man of childbearing age and valproate has been prescribed for you, please refer to the paragraph below, *"Pregnancy, breast-feeding and fertility – important information for adolescents and men of childbearing age"*.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT DEPAKINE IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group: ANTIEPILEPTIC

This medicine is used to treat various types of epilepsy, as a replacement for the oral form when the oral form cannot be used temporarily.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE DEPAKINE

Contra-indications

Do not use Depakine

- if you are pregnant, unless no other epilepsy treatment works for you (see below "Pregnancy, breast-feeding and fertility – Important advice for women"),
- if you are a woman of childbearing age, unless no other epilepsy treatment works for you and you are able to follow all the measures of the pregnancy prevention plan (see below "Pregnancy, breast-feeding and fertility – Important advice for women"),
- if you are allergic to the active substance (sodium valproate) or any of the other ingredients of this medicine (listed in section 6),
- if you are allergic to a medicine in the same family as valproate (valproate semisodium, valpromide),
- if you have liver disease (acute or chronic hepatitis),
- if you or a member of your family have ever had serious liver disease, particularly related to use of a medicine,
- if you have hepatic porphyria (hereditary liver disease),
- if you have a genetic problem causing a mitochondrial disorder (e.g. Alpers-Huttenlocher Syndrome),
- if you have a known metabolic disorder, such as a urea cycle disorder (see "Warnings and precautions"),
- if you have a carnitine deficiency (a very rare metabolic disease), which is not being treated,
- if you are currently taking the following medicine:
  - St. John's Wort (plant used to treat depression).

Warnings and precautions

This medicine can, in very rare cases, cause liver damage (hepatitis) or pancreas damage (pancreatitis), which can be serious and life-threatening.
Your doctor will prescribe blood tests to regularly monitor your liver function, particularly during the first 6 months of treatment.
Inform your doctor immediately if any of the following signs appear:
- sudden fatigue, loss of appetite, exhaustion, drowsiness, swelling of the legs, general malaise,
- repeated vomiting, nausea, stomach or bowel pain, yellow colour of the skin or eyes (jaundice),
- recurrence of epileptic seizures even though you are taking your treatment correctly.
- fever and difficulty breathing.
- The risk of liver damage is increased if Depakine is given to children under 3 years of age, people taking other antiepileptic drugs at the same time, or people with another neurological or metabolic disorder and severe forms of epilepsy.
- If, during treatment with Depakine, you or your child experience(s) problems with balance and coordination, feeling of lethargy or decreased alertness or vomiting, tell your doctor immediately. This may be due to an increased amount of ammonium in the blood.

Talk to your doctor before using this medicine
- If you have kidney disease (renal failure).
- If you have systemic lupus erythematosus (rare disease).
- If you know or if your doctor suspects that there is a genetic problem caused by a mitochondrial disease in your family, due to a risk of damage to your liver.
- If you are suspected of suffering from metabolic disorders, including hereditary disorders caused by an enzyme deficiency of the "urea cycle disorder" type, due to a risk of increased ammonium levels in the blood.
- If you suffer from a rare disease (hereditary metabolic disease) called "carnitine palmitoyltransferase II deficiency", because you have an increased risk of serious muscle disorders (rhabdomyolysis).
- If you have a dietary deficiency of carnitine, which is contained in meat and dairy products, especially in children under 10 years of age.
- If you have a carnitine deficiency and you are taking carnitine.
- If you are scheduled to have surgery, you must inform the medical personnel that you are using this medicine.
- At the start of treatment, your doctor will check that you are not pregnant and that you have a method of contraception (see "Pregnancy").
- As with other antiepileptics, using this medicine can lead to your seizures worsening or becoming more frequent; you may even experience a different type of seizure.
- This medicine can cause weight gain. Your doctor will recommend that you take certain dietary measures and will monitor your weight.
- Self-destructive or suicidal thoughts have also been observed in a small number of people treated with antiepileptics such as Depakine. If you have these kinds of thoughts, contact your doctor immediately.
- Inform your doctor if you have symptoms such as tremor, stiffness of the limbs and difficulty walking (extrapyramidal disorders) or memory and mental capacity disorders. He or she will try to find out whether they are caused by an underlying disease or by Depakine. It may be necessary to stop treatment.

Inform your doctor if your child is taking another antiepileptic treatment or has another neurological or metabolic disease or severe forms of epilepsy.

Other medicines and Depakine

Some medicines may alter the effects of valproate and vice versa.

You must never use this medicine if you are taking the following medicine:
- St. John's Wort (plant-based medicine used to treat depression).

Unless your doctor or pharmacist tells you otherwise, you must not use this medicine if you are taking, have recently taken or might take the following medicines:
- lamotrigine (another medicine used to treat epileptic seizures);
- penems (carbapenems) (antibiotics used to treat bacterial infections).

Tell your doctor if you are taking:
- acetazolamide-containing medicines (medicines used to lower eye pressure or carbon dioxide levels in the blood).
- antibiotics (medicines containing aztreonam or rifampicin),
- other antiepileptic medicines (medicines containing carbamazepine, felbamate, phenytoin, fosphenytoin, primidone, phenobarbital, rufinamide, topiramate or zonisamide),
- nimodipine: Depakine can increase the effects of nimodipine (medicine used to prevent complications that can occur after bleeding in the brain).
- oestrogen-containing products (including some birth control pills).
- propofol (anaesthetic medicine).
- zidovudine-containing medicines (medicines used to treat HIV infection (Human Immunodeficiency Virus)).
- medicines containing lithium (medicines used to treat mood disorders);
- medicines containing metamizole (medicines used to treat pain and fever);
- methotrexate (used to treat cancer and inflammatory diseases);
- salicylates (including aspirin);
- cannabidiol (used to treat epilepsy and other illnesses);
- some anti-infectives containing pivalate (for example: pivampicillin, adefovir dipivoxil).

Specifically in children under 3 years of age, you must avoid giving medicines containing salicylates (including aspirin) during treatment.
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Depakine with food, drink and alcohol

Use of alcoholic beverages is not recommended during treatment with Depakine.

Pregnancy, breast-feeding and fertility

Pregnancy

Important advice for women:
Valproate is harmful to unborn child if taken during pregnancy. Therefore:
- **If you are a female child, female adolescent or woman of childbearing age, your specialist doctor may not prescribe valproate for you unless other treatments are ineffective or not tolerated. If no other treatment is possible, valproate will be prescribed for you and dispensed under the very strict conditions described below.**
- **Make sure you read the patient guide that you will receive from your specialist doctor. Your doctor will discuss the Annual Risk Acknowledgment Form and will ask you to sign it and keep it. You must show it to the pharmacist every time you pick up your medicine, along with the doctor's prescription. This Form certifies that the risks have been explained to you and that you agree to comply with the conditions below. Your pharmacist will also give you a Patient Card to remind you of the risks associated with taking valproate during pregnancy.**

You must not use Depakine:
- if you are pregnant, unless no other epilepsy treatment works for you.
- if you are a woman of childbearing age, unless no other epilepsy treatment works for you and you are able to follow all the steps of the Pregnancy Prevention Plan.

Risks related to taking valproate during pregnancy
- Talk to your specialist doctor immediately if you are planning to have a baby, are pregnant or think you might be pregnant.
- Valproate carries a risk for the unborn child if taken during pregnancy. The higher the dose, the greater the risks; however, **all doses carry a risk**, including when valproate is used in combination with other medicines to treat epilepsy
- When taken by pregnant women, valproate can cause serious birth defects and may have a harmful effect on the development (intellectual, motor, behavioural) of the growing child.
- The most commonly reported birth defects include spina bifida (bone malformation of the spinal cord), malformations of the face, upper lip and palate, skull, heart, kidneys, urinary tract and genitals and damage to the limbs, and multiple combined malformations affecting several organs and parts of the body. The birth defects may lead to handicaps, which may be severe.
- Hearing disorders and hearing loss have been reported in children exposed to valproate during pregnancy.
- Eye malformations have been reported in children exposed to valproate during pregnancy in association with other birth defects. These eye malformations may affect vision.
- If you take valproate during pregnancy, you have a higher risk than other women of having a child with birth defects that require medical treatment. Since valproate has been used for many years, **it is known that nearly 11 out of 100 babies born to mothers taking valproate have birth defects, compared to 2 to 3 out of 100 babies in the general population.**
- **It is estimated that up to 30–40% of pre-school children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slower to walk and/or talk, and/or have a lower IQ than other children, and/or have difficulty with language and/or memory.**
- **Autistic spectrum disorders are more often diagnosed in children exposed to valproate during pregnancy.**
- **There is evidence that children exposed to valproate during pregnancy have an 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 while taking valproate.** If you decide later you want to have a baby you must not stop taking your medicine or your method of contraception until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact the doctor once your child using valproate experiences her first monthly period.
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of contraception that is the most appropriate for you.

Please choose the situation that applies to your case in the list below and read the corresponding paragraph:
- ○ I AM STARTING TREATMENT WITH DEPAKINE
- ○ I AM TAKING DEPAKINE AND NOT PLANNING TO HAVE A BABY
- ○ I AM TAKING DEPAKINE AND PLANNING TO HAVE A BABY
- ○ I AM PREGNANT AND I AM TAKING DEPAKINE

I AM STARTING TREATMENT WITH DEPAKINE

If this is the first time you have been prescribed Depakine, your specialist doctor will have explained the risks of the treatment for the unborn child if you become pregnant. **Once you are able to have a baby, you must use at least 1 effective method of contraception without interruption throughout your treatment with Depakine.** Talk to your doctor, gynaecologist or family planning clinic if you need advice on contraception.

Key messages:
- Before starting treatment, your doctor will have to make sure that no treatment other than valproate works for you.
- Before starting treatment, your doctor will ask you to do a pregnancy test. Pregnancy must be excluded before start of treatment with Depakine with the result of a pregnancy test, confirmed by your doctor.
- You must use at least 1 effective method of birth control (preferably an intrauterine device or a contraceptive implant) or 2 effective methods that work differently (for example, the Pill and a condom) during your entire treatment with Depakine.
- You must discuss the appropriate methods of birth control with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on contraception.
- You must get regular (at least annual) appointments with a specialist doctor experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your specialist doctor you want to have a baby before stopping your contraception.
- Schedule an urgent appointment with your specialist doctor experienced in the treatment of epilepsy if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKINE AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with Depakine but you are not planning to have a baby make sure you are using at least 1 effective method of contraception without interruption during your entire treatment with Depakine. Talk to your doctor, gynaecologist or family planning clinic if you need advice on contraception.

Key messages:
- Your specialist doctor must check regularly (at least once a year) whether any treatment other than valproate works for you.
- You must use at least 1 effective method of contraception (preferably an intrauterine device or a contraceptive implant) or 2 effective methods that work differently (for example, the Pill and a condom) during your entire treatment with Depakine.
- You must discuss the appropriate methods of birth control with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on contraception.
- You must get regular (at least annual) appointments with a specialist doctor experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby before stopping your contraception.
- Schedule an urgent appointment with your specialist doctor experienced in the treatment of epilepsy if you are pregnant or think you might be pregnant.

I AM TAKING DEPAKINE AND PLANNING TO HAVE A BABY

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. **If you are planning to have a baby, first schedule an appointment with your specialist doctor experienced in the management of epilepsy.**
Do not stop taking Depakine or your contraception until you have discussed this with your doctor. Your doctor will advise you further and refer you to a specialist doctor experienced in the treatment of epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.
Your specialist should do everything possible to stop the Depakine treatment long before you become pregnant, in order to ensure that your illness is stable. In exceptional circumstances when this is not possible, see the following paragraph ("I AM PREGNANT AND I AM TAKING DEPAKINE").
Ask your doctor about taking folic acid if you are planning to become pregnant. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking Depakine unless your doctor tells you to.
- Do not stop using your methods of contraception before you have talked to your specialist doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your specialist doctor. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your specialist doctor should try everything to stop the treatment with Depakine a long time before you become pregnant.
- Schedule an urgent appointment with your specialist doctor experienced in the management of epilepsy if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM TAKING DEPAKINE

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with intellectual and motor and behavioural disorders which can be seriously debilitating. Do not stop taking Depakine, unless your doctor tells you to as your condition may become worse. **Schedule an urgent appointment with your specialist doctor experienced in the treatment of epilepsy if you are pregnant or think you might be pregnant:**
- your doctor will advise you further.
- your doctor should try everything possible to stop the treatment and assess all the other options for treatment.

In the exceptional circumstances when Depakine is the only available treatment option during pregnancy:
- Your doctor may refer you to a specialist so that you and your partner receive counselling and support regarding the valproate-exposed pregnancy.
- Your specialist doctor will try to decrease the prescribed dose.
- You will be closely monitored, both for the treatment of your illness and to monitor the development of your unborn child.
- Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.
- **Before the birth:** your doctor will prescribe certain vitamins for you so that this medicine does not cause bleeding during the first few days of your baby's life or bone deformities.
- **After the birth:** an injection of vitamin K may also be prescribed for your baby after birth to prevent bleeding.
- **In children:** inform the doctor(s) monitoring your child that you were treated with valproate during pregnancy. He or she will implement strict monitoring of your child's neurological development in order to provide your child with specialized care as early as possible if necessary.

Key messages:
- Schedule an urgent appointment with your specialist doctor experienced in the management of epilepsy if you are pregnant or think you might be pregnant.
- Do not stop taking Depakine unless your specialist doctor tells you to.
- Your specialist doctor experienced in the treatment of epilepsy must evaluate all of the options for stopping this treatment.
- Your specialist doctor must give you complete information about the risks related to taking Depakine during pregnancy, especially the risks of malformations (birth defects) and of development disorders (intellectual, motor and behavioural) in children.
- Make sure you are referred to a specialist doctor for prenatal monitoring in order to detect possible occurrences of birth defects.
- Inform the doctors who will be monitoring your child that you took Depakine during your pregnancy. They will implement strict monitoring of the child's neurological development.

Important information for adolescents men of childbearing age

Potential risks related to taking valproate in the 3 months before conceiving a child
One study suggests a potential risk of mental and/or motor development disorders (developmental problems in early childhood) in children whose fathers were treated with valproate in the 3 months before conception. In this study, approximately 5% of children born to fathers treated with valproate presented with developmental disorders, whereas in the comparison group in which fathers were treated with other drugs, lamotrigine or levetiracetam, approximately 3% of children had such disorders. The risk is not known for children born to fathers who have discontinued treatment with valproate more than 3 months before conception (required time to form new spermatozoa). The study has limitations; it is therefore not certain whether the increased risk of motor and mental development disorders suggested by this study is caused by valproate. The number of patients included in the study was not sufficient to determine the specific types of motor and mental development disorders that children are likely to develop.

As a precautionary measure, your doctor will discuss with you:
- The potential risk of developmental disorders in children born to fathers treated with valproate.
- The need to consider effective contraception for you and your partner during treatment and for 3 months after stopping valproate.
- The need to consult your doctor when planning to conceive a child and before stopping contraception.
- The possibility of considering other treatments that are more appropriate to treat your disease, depending on your individual situation.
- You must not donate sperm during treatment with valproate or any of its derivatives, and for at least three months after it has been discontinued.

If you are planning to have a baby, talk to your doctor.
If your partner becomes pregnant while you were taking valproate in the 3 months prior to conception and you have any questions, contact your doctor. Do not stop your treatment without talking to your doctor because if you stop it by yourself, it would expose you to the recurrence of your symptoms.
You must consult your doctor regularly. During this consultation, your doctor will discuss with you the precautions associated with the use of valproate and the possibility of other treatments for your disease, depending on your individual situation.
Read the patient guide given to you by your doctor. A patient card will also be given to you by your pharmacist to remind you of the potential risks of valproate.

Breast-feeding

You must not breast-feed during treatment with this medicine unless otherwise indicated by your doctor.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Depakine may cause drowsiness, especially if taken in combination with other antiepileptic drugs or medicines that can increase drowsiness.
If you experience this effect and if your condition is not under control yet and you continue to have seizures, you must not drive or operate machinery.

Depakine 400 mg/4 ml preparation for IV injection contains sodium

This medicine contains 55 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.8% of the recommended maximum daily dietary intake of sodium for an adult. You must take this into account if you are on a salt-free or low-salt diet.

3. HOW TO USE DEPAKINE

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Instructions for proper use

Girls and women of childbearing potential
Depakine treatment must be started and supervised by a doctor specialized in the treatment of epilepsy. This treatment must not be prescribed in female children, female adolescents or women able to have a baby unless other treatments are ineffective or not tolerated. If no other treatment is possible, valproate will be prescribed for you and dispensed under very strict conditions (given in the Pregnancy Prevention Program). A specialist must re-evaluate the need for treatment at least once per year.

Adolescents and men of childbearing potential
It is recommended that treatment with Depakine be initiated and supervised by a doctor specialized in the management of epilepsy - see section 2 « Important information for adolescents and men of childbearing potential ».

Posology

The daily dose, frequency and administration times will be decided on for you and checked by your doctor.
Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

Patients with kidney disorders

Your doctor may decide to adjust your dose.

Method of administration

A healthcare professional will prepare and inject this medicine into your vein either by direct injection or by infusion.
This medicine must not be injected into a muscle (intramuscular route), as it could cause side effects (risk of local tissue necrosis).
After reconstitution: clear to slightly opalescent liquid.

Duration of treatment

Do not stop using this medicine without your doctor's advice. The doctor will decide how long the treatment should be used for.

If you have been given more Depakine than you should

Talk to your doctor or go to the emergency room immediately.

If you stop using Depakine

Do not stop using Depakine without asking your doctor's advice. Treatment must be stopped gradually. If you stop using Depakine suddenly or before your doctor asks you to, you will be exposed to a higher risk of seizures.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any of the following serious side effects. You may need urgent medical care:
- Problems with balance and coordination, feeling of lethargy or poorer alertness, combined with vomiting. This may be due to an increase in the amount of ammonium in your blood,
- liver damage (hepatitis) or pancreas damage (pancreatitis), which may be serious and life-threatening, and that can start suddenly with fatigue, loss of appetite, exhaustion, drowsiness, nausea, vomiting and stomach pain,
- allergic reaction:
  - ○ sudden swelling of the face and/or neck that can cause difficulty breathing and be life-threatening (angioedema),
  - ○ serious allergic reaction (drug hypersensitivity syndrome) including several symptoms such as fever, skin rash, increased size of lymph nodes, liver damage, kidney damage and abnormal blood test results such as an increase in the number of certain white blood cells (eosinophils),
- raised skin rash, sometimes with blisters that can also affect the mouth (erythema multiforme), blisters with detachment of the skin that can rapidly spread to the entire body and be life-threatening (toxic epidermal necrolysis, Stevens-Johnson syndrome).

Other possible side effects:
- birth defects and intellectual and motor development disorders (see section 2, "Pregnancy, breast-feeding and fertility").

Tell your doctor or pharmacist immediately if any of the following side effects become serious or last more than a few days. You may need urgent medical treatment:

Very common (may affect more than 1 in 10 people):
- nausea,
- tremor.

Common (may affect up to 1 in 10 people):
- at the beginning of treatment: vomiting, stomach ache, diarrhoea,
- weight gain,
- headache,
- drowsiness,
- convulsions,
- memory disorders,
- confusion, aggressiveness, agitation, attention deficit disorders, hallucinations (seeing, hearing or feeling things that are not there),
- extrapyramidal disorders (a group of symptoms such as tremor, stiffness of the limbs and difficulty walking)*,
- leakage of urine (urinary incontinence),
- rapid and uncontrollable eye movements,
- hearing loss,
- gum disorders (gingival problems), in particular an increase in gum size (gingival hypertrophy),
- painful, swollen mouth, mouth ulcers and burning sensation in the mouth (stomatitis),
- hair loss,
- menstrual problems (irregular menstruation),
- bleeding,
- nausea or dizziness,
- nail and nail bed disorders,
- decrease in the number of platelets (thrombocytopenia), decrease in the number of red blood cells (anaemia),
- decrease in the amount of sodium in the blood (hyponatremia, syndrome of inappropriate antidiuretic hormone secretion).

Uncommon (may affect up to 1 in 100 people):
- impaired alertness that may go as far as transient coma, regressing after the dose is decreased or the treatment stopped,
- difficulty coordinating movements,
- reversible parkinsonism*,
- sensation of numbness or prickling in the hands and feet,
- abnormal hair texture, change in hair colour, abnormal hair growth,
- rash or hives on the skin,
- excessive hair growth, particularly in women, virilism, acne (hyperandrogenism),
- decreased body temperature (hypothermia),
- swelling of the extremities (oedema),
- amenorrhea (lack of menstrual period),
- worsening and increased frequency of convulsions; onset of a different type of convulsion,
- breathing difficulty and pain, due to inflammation of the protective membranes of the lungs (pleural effusion),
- decrease in the numbers of all blood cells: white blood cells, red blood cells and platelets (pancytopenia)
- severe decrease in the number of white blood cells (leukopenia), observed during blood tests, sometimes revealed by fever and difficulty breathing,
- cases of bone disorders have been reported, such as the bones becoming more fragile (osteopenia), a decrease in bone mass (osteoporosis) and fractures. Consult your doctor or pharmacist if you are on long-term treatment with an antiepileptic medicine, if you have a history of osteoporosis or if you are taking corticosteroids,
- blood vessel inflammation.

Rare (may affect up to 1 in 1 000 people):
- male fertility disorders, generally reversible at least 3 months after treatment is discontinued, and possibly reversible after a reduction in the dose. Do not stop your treatment without first talking to your doctor,
- abnormal functioning of the ovaries (polycystic ovary syndrome),
- behavioural disturbances, increased psychomotor activity, learning disabilities,
- auto-immune reaction with painful joints, skin rash and fever (systemic lupus erythematosus),
- decreased thyroid gland activity (hypothyroidism),
- muscle pain, muscle weakness that may be serious (rhabdomyolysis),
- obesity,
- involuntary leakage of urine, usually at night (enuresis),
- kidney damage (kidney failure, tubulointerstitial nephritis) which may manifest as decreased urine output,
- urinating a lot and feeling thirsty (Fanconi syndrome),
- increase in the size of red blood cells (macrocytosis), major decrease in the number of white blood cells (agranulocytosis),
- decreased production of blood cells (bone marrow aplasia), abnormal production of blood cells (myelodysplasia), observed during blood tests, sometimes revealed by fever and difficulty breathing,
- decrease in coagulation factors, abnormal blood coagulation test (increase in INR, increase in activated partial thromboplastin time),
- decrease in the amount of vitamin B8 (biotin)/biotinidase,
- increase in the amount of ammonium in the blood,
- double vision,
- the gradual onset of memory and mental capacity disorders (cognitive disorders, dementia)*. These problems decrease a few weeks to a few months after treatment is discontinued.

Frequency not known
- decreased carnitine level (observed in blood or muscle tests).

Do not stop your treatment without first talking to your doctor.

*These symptoms can be associated with brain imaging signs (cerebral atrophy).

Not known (cannot be estimated from the available data)
- risk of local tissue necrosis if injections are received repeatedly.

Additional side effects in children

Some side effects of valproate occur more frequently in children or are more serious than in adults. These lead to liver damage, inflammation of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity, and learning disorders.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE DEPAKINE

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton.
The expiry date refers to the last day of that month.
Store below 30°C.
After opening/reconstitution/dilution: the medicinal product must be used immediately.
After reconstitution the product is a clear to slightly opalescent liquid.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Depakine 400 mg/4 ml preparation for IV injection contains
- The active substance is:
  Sodium valproate .....400 mg
  For 4 mL of reconstituted solution.
- The other ingredients are:
  Solvent: water for injections.

What Depakine 400 mg/4 ml preparation for IV injection looks like and contents of the pack

This medicine is supplied as an preparation for IV injection. Box of 1, 4 or 80 vials and ampoules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

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GENERAL ADVICE

Epilepsy is a neurological disease. It is an expression of acute and temporary abnormal function of electrical activity in the brain, resulting in epileptic seizures. The seizures may be repeated throughout a certain period of an individual's life. There are many forms of expression of these seizures and they may progress in many different ways:
there is not **one type** of epilepsy but **several** different types.
Similarly, there is not one treatment but several possible treatments: your doctor will prescribe the one best suited to you.
To ensure that this medicine is effective, it is essential that you follow your doctor's recommendations and comply with:
- prescribed daily doses,
- the time of the doses,
- treatment duration, generally long-term,
- lifestyle recommendations: avoid overwork, lack of sleep and alcohol.

Changing the doses and, especially, suddenly stopping the treatment, can cause seizures to recur.

DO NOT FORGET TO TAKE YOUR MEDICINE WITH YOU IF YOU TRAVEL.