PACKAGE LEAFLET: INFORMATION FOR THE USER

Depakine® 57.64 mg/ml, syrup

sodium valproate

▼ 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. See the end of section 4 for how to report side effects.

WARNING

Children exposed to valproate *in utero* have a high risk of serious developmental disorders (mental and physical) and behavioral disturbances (up to 30 to 40% of cases) and/or birth defects (approximately 10% of cases).

If you are a female child, a female adolescent, a woman of childbearing age or if you are pregnant, your doctor will only prescribe valproate for you if other treatments are not effective or not tolerated.

If you are a female of childbearing age you should use an effective method of contraception throughout your treatment. If you are planning a pregnancy, you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet.

Tell your doctor at once if you become pregnant or think you might be pregnant.

Read this leaflet carefully before you start taking 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 symptoms seem 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 TO

Depakine belongs to a family of medicines called antiepileptics.

This medicine is used to treat various types of seizures in adults and children. It is also used in children to prevent fever-related seizures.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE DEPAKINE

Contraindications:

Never take Depakine:

- if you are allergic to the active substance of this medicine (sodium valproate) or to any of the other ingredients in Depakine. For the list of ingredients, see Section 6,
- if you are allergic to a medicine in the same family as valproate (divalproate, 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 are currently taking the following medicines:
  - mefloquine (medicine used to treat malaria),
  - St. John's Wort (plant used to treat depression).

If your doctor has informed you that you have an intolerance to certain sugars, contact him or her before taking this medicine.

Appropriate precautions for use; Special warning

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 color of the skin or eyes (jaundice).
- recurrence of epileptic seizures even though you are taking your treatment correctly.

- Before taking this medicine, tell your doctor if you have kidney disease (renal insufficiency), systemic lupus erythematosus (rare disease) or hereditary enzyme deficiencies, particularly an enzyme deficiency of the urea cycle that can cause increased amounts of ammonium in the blood or if you know that there is a genetic problem causing a mitochondrial disorder in your family.
- If you are scheduled to have surgery, you must inform the medical personnel that you are taking 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 Section "Pregnancy»).
- Consult your doctor immediately if the frequency of seizures increases or if you 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.
- If you have carnitine palmitoyltransferase type II (CPT-II) deficiency (rare hereditary metabolic disease), the risk of developing serious muscle problems (rhabdomyolysis) is higher with this medicine.

Other medicines and Depakine

You must never take this medicine if you are taking any of the following medicines:
- mefloquine (medicine used to treat malaria),
- edicine used to treat depression).

You must tell your doctor if you are taking lamotrigine (another medicine used to treat epileptic seizures) or penems (antibiotics used to treat bacterial infections).

Specifically in children under 3 years of age, you must avoid giving medicines that contain aspirin during treatment.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Depakine with food and alcohol

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

Pregnancy

Important advice for women

If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you. Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but **all doses carry a risk**.
- **Children exposed to valproate in utero have a high risk of serious birth defects and developmental disorders (mental and physical) and behavioral disturbances.** Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial, upper lip, palate and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- 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. Because valproate has been used for many years we know that in women who take valproate around **10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.**
- **It is estimated that up to 30-40% of preschool children whose mothers took 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.**
- To date, limited data indicate that children may be more likely to develop symptoms of **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 child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. Taking folic acid supplements before pregnancy can lower the risk of neural tube closure defects and early miscarriage that exists with all pregnancies. However, prevention of birth defects associated with valproate use by folic acid is not proven to date.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. **If you are of childbearing age, you must use an effective method of contraception throughout your treatment.** Talk to your general practitioner, gynecologist or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your general practitioner, gynecologist or family planning clinic if you need advice on contraception.

Key messages:
- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you 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 doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Taking folic acid supplements before pregnancy can lower the risk of neural tube closure defects and early miscarriage that exists with all pregnancies. However, prevention of birth defects associated with valproate use by folic acid is not proven to date.

Key messages:
- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy is controlled and the risks to your baby are reduced.
- Tell your doctor at once if you are pregnant or think you might be pregnant

UNPLANNED PREGNANCY WHILE CONTINUING TREATMENT

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with mental and physical development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant **contact your doctor at once**. Do not stop taking your medicine until your doctor tells you to.

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.

Key messages:
- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

Make sure you read and understand the patient booklet and sign the treatment consent form which should be given to you by your doctor. Ask your doctor or pharmacist for advice.

Breast-feeding

You must not breast-feed during treatment with this medicine unless otherwise indicated by your doctor.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Depakine can cause drowsiness, particularly if it is taken in combination with other antiepileptics or medicines that can increase drowsiness.
If you experience this effect or if your condition is not under control yet and you continue to have seizures, you must not drive or use machines.

Depakine contains:
This medicine contains sucrose and sorbitol. It is therefore not recommended if you have fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency (rare hereditary diseases). If your doctor has informed you that you have an intolerance to certain sugars, contact him or her before taking this medicine.
This medicine contains 13.88 mg of sodium per 100 mg of sodium valproate. You must take this into account if you are on a salt-free or low-salt diet.

3. HOW TO TAKE DEPAKINE

Depakine treatment must be started and supervised by a doctor specialized in the treatment of epilepsy.
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dosage
- The daily dose to be administered is determined and controlled individually by your doctor.
- The dose is generally divided into:
  - 2 doses per day in children under 1 year of age,
  - 3 doses per day in adults and children over 1 year of age.
- The dose should preferably be taken during meals.

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

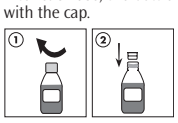
Method of administration
- The bottle of syrup comes with a syringe for oral administration (white plunger) that is inserted into the adaptor cap.
- Administer the syrup with the syringe in this box only.

Opening the bottle
To open the bottle, push down on the child-safety cap and turn. The bottle must be closed again after each use.

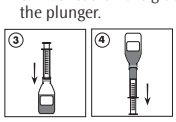
To open the bottle:
1. Press down on the child-safety cap.
2. And turn at the same time.

When opening the bottle for the first time:
1. Open the bottle (see description on the diagram above).
2. Place the adaptor tip of the syringe for oral administration on the opening of the bottle and push down to insert it.
   The adaptor tip must remain in the bottle like this for the duration of use.

After each use, the bottle must be closed again with the cap.



Using the syringe for oral administration and its white plunger:
3. Push the syringe into the adaptor tip.
4. Firmly hold the adaptor tip and the neck of the bottle together. Turn the bottle and syringe upside down together. Pull the plunger downwards to the prescribed dose. The dose can be read on the graduation lines of the plunger.



5. Turn the bottle and the syringe right side up again. Withdraw the syringe from the adaptor tip.
6. Close the bottle again with the cap.

7-8. After administration of the syrup, the syringe must be cleaned by pumping water in and out of it 2 to 3 times.

Duration of treatment
Do not stop taking this medicine without asking your doctor's advice.

If you take more Depakine than you should:
Consult your doctor or an emergency medical service immediately.

If you forget to take Depakine:
Do not take a double dose to make up for a forgotten dose.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Depakine can cause side effects, although not everybody gets them.
Consult your doctor or pharmacist immediately if you experience any of the following effects:
- 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 bowel 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:
- Congenital birth defects and mental and physical development disorders (see Section 2 "Pregnancy and breast-feeding»).

- **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 pain, diarrhea,
- weight gain,
- headache,
- drowsiness,
- seizures,
- memory disorders,
- confusion, aggression, 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) that are sometimes irreversible. In some cases, the Parkinsonian syndrome may be reversible,
- rapid and uncontrollable eye movements,
- hearing loss,
- gum disorders (gingival disorders), in particular an increase in gum size (gingival hypertrophy),
- painful, swollen mouth, sores and burning sensation in the mouth (stomatitis),
- hair loss,
- menstrual disorders (menstrual irregularity),
- bleeding,
- decrease in the number of platelets (thrombocytopenia), decrease in the number of red blood cells (anemia),
- 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,
- sensation of numbness or prickling in the hands and feet,
- abnormal hair texture, change in hair color, abnormal hair growth,
- rash or hives on the skin,
- excessive hair growth, particularly in women, virilism, acne (hyperandrogenism),
- decreased body heat (hypothermia),
- swelling of the extremities (edema),
- amenorrhea (lack of menstrual period),
- 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), decrease in the number of white blood cells (leukopenia),
- 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 receiving long-term treatment with an antiepileptic drug, if you have a history of osteoporosis or if you are taking corticosteroids.

- **Rare (may affect up to 1 in 1000 people):**
- memory and mental capacity disorders that appear gradually (cognitive disorders, dementia) and regress a few weeks to a few months after stopping treatment,
- difficulty or inability to retain urine (enuresis, urinary incontinence),
- reduced sperm motility,
- abnormal functioning of the ovaries (polycystic ovary syndrome),
- behavioral 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),
- kidney damage (kidney failure, tubulointerstitial nephritis),
- increase in the size of red blood cells (macrocytosis), major decrease in the number of white blood cells (agranulocytosis),
- reduced production of blood cells (bone marrow aplasia), blood cell production abnormality (myelodysplasia),
- decrease in coagulation factors, abnormal blood coagulation test results (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.

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 OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not use this medicine after the expiry date which is stated on the box after {MM/YYYY}. The expiry date refers to the last day of that month.
This medicine can be stored for one month after opening at a temperature not exceeding 25°C.
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. FURTHER INFORMATION

What Depakine contains

The active substance is:
Sodium valproate .....57.64 mg for 1 ml.

The other ingredients are:
Methyl parahydroxybenzoate, propyl parahydroxybenzoate, sucrose, 70% sorbitol solution, glycerol, artificial cherry flavor, concentrated hydrochloric acid, sodium hydroxide, purified water.

What Depakine looks like and contents of the pack
This medicine is supplied as a syrup in 150 ml bottles with syringe for oral administration.

Marketing Authorization Holder
sanofi-aventis France
1-13, boulevard Romain Rolland
75014 Paris - France

Manufacturer
Unither Liquid Manufacturing
1-3 allée de la Neste
Z.I. d'en Sigal
31770 Colomiers - France

This leaflet was last approved in: April 2015

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 FORGER TO TAKE YOUR MEDECINE WITH YOU IF YOU TRAVEL