

Package leaflet: Information for the patient

Syonell 250mg Gastro-Resistant tablets Syonell 500mg Gastro-Resistant tablets valproate semisodium

▼ 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

Syonell, valproate semisodium, can seriously harm an unborn child when taken during pregnancy. If you are a female able to have a baby, you must use effective method of birth control (contraception) without interruptions during your entire treatment with Syonell. 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 Syonell unless your doctor tells you to as your condition may become worse.

Read all of 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 . Do not pass it on to others. It may harm them, even if their symptoms 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 Syonell is and what it is used for
2. What you need to know before you take Syonell
3. How to take Syonell
4. Possible side effects
5. How to store Syonell
6. Contents of the pack and other information

1. What Syonell is and what it is used for

The name of your medicine is Syonell 250mg Gastro-Resistant tablets or 500mg Gastro-Resistant tablets. Syonell tablets contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.

Syonell can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression). Syonell can be used when lithium cannot be used.

2. What you need to know before you take Syonell

Do not take Syonell if:

- You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of this medicine (listed in section 6)
Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- You have liver problems or you or your family have a history of liver problems, especially if caused by taking a medicine
- You have a rare illness called porphyria which affects your metabolism
- You have a known metabolic disorder, i.e. a urea cycle disorder
- You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)
- You are pregnant (see Pregnancy, breast-feeding and fertility-important advice for women' below)

If you are a woman able to have a baby, you must not take Syonell, unless you use an effective method of birth control (contraception) at all times during your treatment with Syonell. Do not stop taking Syonell or your contraception, until you have discussed this with your doctor. Your doctor will advise you further (see below under "Pregnancy, breast-feeding and fertility – Important advice for women").

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Syonell.

Warnings and precautions

A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

In patients with epilepsy convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.

Talk to your doctor or pharmacist before taking your medicine if:

- You are changing from another medicine that contains valproate
- The person taking this medicine is less than 18 years old
- You have fits (epilepsy), a brain disease or a metabolic condition affecting your brain.
- You have problems with your pancreas.
- You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests
- You have a carnitine palmitoyltransferase type II deficiency
- You have kidney problems
- You have a 'urea cycle disorder' where too much ammonia builds up in the body
- You have an illness called 'systemic lupus erythematosus (SLE)' - a disease of the immune system which affects the skin, bones, joints and internal organs
- You 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 Syonell.

Weight gain

Taking Valproate semisodium may make you put on weight. Talk to your doctor about how this will affect you.

Other medicines and Syonell

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Syonell can affect the way some other medicines work. Also, some medicines can affect the way Syonell works.

In particular, do not take and check with your doctor if you are taking any of the following:

- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Syonell works or Syonell can affect the way some of these medicines work:

- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine
- Zidovudine and protease inhibitors such as lopinavir and ritonavir - used for HIV infection
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Syonell and carbapenems should be avoided because it may decrease the effect of your medicine
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Cholestyramine - used for lowering blood cholesterol levels
- Nimodipine
- Propofol – used for anaesthesia
- Oestrogen-containing products (including some birth control pills).

Syonell with alcohol

Alcohol intake is not recommended during treatment.

Pregnancy, breast-feeding and fertility

Important advice for women

- You must not use Syonell if you are pregnant.
- If you are a woman able to have a baby, you must not take Syonell, unless you use an effective method of birth control (contraception) during your entire treatment with Syonell.
- Do not stop taking Syonell or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy

- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. The most frequently reported birth defects 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 and multiple associated malformations affecting several organs and parts of the body. Birth defects may result in disabilities which may be severe.
- Hearing problems or deafness 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 congenital malformations. 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. 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 bipolar disorder.
- 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 during pregnancy and there is some evidence that children exposed to 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 valproate. 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.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- 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 birth control (contraception) that is the most appropriate for you.
- Ask your doctor about taking folic acid when trying for a baby. 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.

Please choose the situations which apply to you and read the descriptions below:

- **I AM STARTING TREATMENT WITH SYONELL**
- **I AM TAKING SYONELL AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING SYONELL AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING SYONELL**

I AM STARTING TREATMENT WITH SYONELL

If this is the first time you have been prescribed Syonell your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby you will need to make sure you use an effective method of birth control (contraception) without interruption throughout your treatment with Syonell. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:

- Pregnancy must be excluded before start of treatment with Syonell with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Syonell.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of 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.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING SYONELL AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with Syonell but you don't plan to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Syonell. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:

- You must use an effective method of birth control (contraception) during your entire treatment with Syonell.

- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder. During this visit your doctor will make sure you are well aware of 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.
- Tell your doctor **immediately** if you are pregnant or think you might be pregnant.

I AM TAKING SYONELL AND PLANNING TO HAVE A BABY

If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking Syonell or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

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. Your doctor will refer you to a specialist experienced in the management of bipolar disorder, 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 may decide to change the dose of Syonell, switch you to another medicine, or stop treatment with Syonell, a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when trying for a baby. 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 Syonell unless your doctor tells you to.
- Do not stop using your method of birth control (contraception) before you have talked to your 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 doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with Syonell a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING SYONELL

Do not stop taking Syonell, unless your doctor tells you to as your condition may become worse. Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

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. You will be referred to a specialist experienced in the management of bipolar disorder, so that alternative treatment options can be evaluated. You and your partner should receive counselling and support regarding the valproate exposed pregnancy.

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:

- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking Syonell unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of bipolar disorder to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Syonell during pregnancy, including malformations and developmental effects in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

Newborn babies of mothers who took valproate during pregnancy may have:

- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar).
- Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines

You may feel sleepy, confused or dizzy while taking this medicine. If this happens, do not drive or use any tools or machines.

Syonell contains sodium:

Syonell 250mg Gastro-Resistant tablets contains 18.51 mg sodium (main component of cooking/table salt) in each tablet. This is equivalent to 0,9% of the recommended maximum daily dietary intake of sodium for an adult per tablet.

Syonell 500mg Gastro-Resistant tablets contains 37.03 mg sodium (main component of cooking/table salt) in each tablet. This is equivalent to 1,8% of the recommended maximum daily dietary intake of sodium for an adult per tablet.

3. How to take Syonell

Always take Syonell exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure.

Syonell treatment must be started and supervised by a doctor specialised in the treatment of bipolar disorders.

How to take your medicine

- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take

Adults (including the elderly)

- **Starting dose is 750mg on the first day. This is usually taken as 2 or 3 divided doses.**
- **The usual dose is then increased** to 1000mg - 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems

- You doctor may decide to adjust your dose.
- Your doctor may decide to lower your dose

Children and adolescents under 18 years of age

Syonell should not be used in children and adolescents under 18 years of age for the treatment of mania

Tests

Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Syonell than you should

If you or someone else has taken more Syonell than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Syonell

If you forget to take a dose at the right time, take it as soon as you remember. **Do not** take a double dose to make up for a forgotten dose.

If you stop taking Syonell

Keep taking your medicine until your doctor tells you to stop. Do not stop taking Syonell just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Syonell, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Syonell can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions

If you have an allergic reaction, stop taking Syonell and see a doctor or go to a hospital straight away. The signs may include: 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.

Stop taking Syonell and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:

- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells

- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can 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.

Other serious side effects which need urgent medical attention:

- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes
- An increase in the number and severity of convulsions in patients with epilepsy

Tell your doctor as soon as possible if you have any of the following side effects:

- Unusual behaviour including being very alert, and sometimes also aggressive, hyperactive and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days

- Swelling of gums or sore mouth
- Nail and nail bed disorders
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Hair disorders (changes in texture, colour or growth), temporary hair loss
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods

- Breast enlargement in men
- Loss of hearing
- Double vision
- Kidney disease, kidney problems, blood in the urine, bedwetting or increased need to pass urine, urinary incontinence (unintentional passing of urine)
- Obesity, weight gain – as your appetite may be increased
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/ hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)

Bone disorders

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Tests

Syonell can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male fertility

Taking Syonell can be a contributing factor in male infertility.

Additional side effects in children

Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, inflammation of the pancreas (pancreatitis), bedwetting (enuresis), renal dysfunction (Fanconi Syndrome), overgrowth of gum tissue, aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Syonell

Keep out of the sight and reach of children.

Do not use after the expiry date which is stated on the blister strip or carton after EXP. The expiry date refers to the last day of that month.

Syonell should be stored below 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Syonell contain

Each oval, pink coloured, gastro-resistant 250mg tablet contains 269.1mg valproate semisodium (equivalent to 250 mg valproic acid) as the active ingredient.

Each oval, pink coloured, gastro-resistant 500mg tablet contains 538.1mg valproate semisodium (equivalent to 500 mg valproic acid) as the active ingredient.

Syonell also contain the following inactive ingredients:

Microcrystalline cellulose, pregelatinised starch, colloidal silicone dioxide, magnesium stearate, low-substituted hydroxypropylcellulose, Opadry White, hypromellose phthalate, triethyl citrate, titanium dioxide (E171) and vanillin.

Syonell are coloured with Allura Red FD&C 40 (E129) and Indigo Carmine FD&C Blue 2 (E132), marked with Opacode Black S-1-17823 (ink) and available in blister packs of 30, 60 and 90 tablets.

Marketing Authorisation Holder and Manufacturer

Lupin Healthcare (UK) Limited
The Urban Building, 2nd floor,
3-9 Albert Street, Slough, Berkshire,
SL1 2BE, United Kingdom.

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