PACKAGE LEAFLET: INFORMATION FOR THE USER

Valpro TAD chrono® 500 mg

Prolonged-release tablets

Active substances: Valproic acid, Sodium Valproate

Read all of this leaflet carefully before you start taking this medicine.
- 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT VALPRO TAD CHRONO 500 MG IS AND WHAT IT IS USED FOR

Valpro TAD chrono 500 mg is used in the treatment of seizure disorders (antiepileptic).

Valpro TAD chrono 500 mg is used
to treat
- seizures emanating from both halves of the brain (generalised seizures, e.g. absences, myoclonic and tonic-clonic seizures)
- seizures emanating from a localised area of the brain (focal seizures) which may spread to both halves of the brain (secondary generalised seizures)
- Valpro TAD chrono 500 mg may be administered to treat other forms of seizures, e.g. seizures with mixed (complex) symptoms and seizures spreading from a localised area of the brain to both halves of the brain (secondary generalised seizures), together with other medications used in the treatment of seizure disorders if these forms of seizure do not respond to standard antiepileptic treatment.

Note:
If a changeover is carried out from previous (non-sustained-release) pharmaceutical forms to Valpro TAD chrono 500 mg, it must be ensured that the serum levels of valproic acid are sufficient.

In the case of small children Valpro TAD chrono 500 mg is only the agent of first choice in exceptional cases; this medication should only be administered to small children with particular caution after careful consideration of the risks and benefits and if possible not together with other medications used in the treatment of seizure disorders.

2. BEFORE YOU TAKE VALPRO TAD CHRONO 500 MG

Do not take Valpro TAD chrono 500 mg
- if you are allergic (hypersensitive) to valproic acid or any of the other ingredients of Valpro TAD chrono 500 mg
- if liver diseases have occurred in your own personal history or that of your family or if you have severely impaired liver or pancreas function
- if any of your brothers and sisters have suffered a fatal outcome during valproic acid treatment in the case of functional disturbances of the liver,
- if you have inherited or acquired disturbances to your haemoglobin metabolism (porphyria)
- if you have impaired blood clotting.

Take special care with Valpro TAD chrono 500 mg
- if you have suffered from damage to your bone marrow in the past; in this case strict medical monitoring is required (checks of the blood count).
- in cases of systemic lupus erythematosus (a reaction of the body's own immune system to its own connective tissue),
- in the case of metabolic disorders, particularly inherited enzyme deficiency disorders. During treatment with medications containing valproic acid there may be an increase in ammonia serum levels (hyperammonaemia).
  You should therefore consult your doctor if any of the following symptoms occur: abnormal fatigue, tiredness, vomiting, reduced blood pressure or an increase in the number of seizures. Your doctor should then determine your ammonia and valproic acid serum levels; if necessary, the Valpro TAD chrono 500 mg dose should be reduced.
  If an existing enzymatic disturbance to the urea cycle is suspected, the ammonia serum levels should be determined before the start of valproic acid therapy.
- In cases of impaired kidney function and/or protein deficiency in the blood, consideration must be given to a rise in free valproic acid in the blood and the dose reduced accordingly.
- Before surgical or dental interventions (e.g. when a tooth is extracted). As during treatment with Valpro TAD chrono 500 mg there may be an increased tendency to bleeding, the attending physician must be informed of the fact that you are taking Valpro TAD chrono 500 mg so that the clotting of your blood can be checked.
- During the simultaneous administration of medications which inhibit blood clotting (e.g. vitamin K antagonists) there may be an increased tendency to bleeding. The clotting behaviour of your blood (Quick value) must therefore be checked at regular intervals.
- Similarly, during the simultaneous administration of acetylsalicylic acid, e.g. ASA, aspirin, there may be an increased tendency to bleeding, so that regular checks of the clotting behaviour of your blood are required (determination of the bleeding time and/or number of blood platelets; see also "Taking other medicines" and "4. Possible side effects").

In such cases you should consult your doctor before the start of treatment. This is also the case if any of the above has applied to you in the past.

Warning:
A small number of people being treated with anti-epileptics such as Valpro TAD chrono 500 mg have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

There have been occasional reports of severe (including fatal) cases of damage to the liver and pancreas. Such damage occurs irrespective of the Valpro TAD chrono 500 mg dose and almost always in the first six months of treatment. This mainly affects children under the age of 15, especially children with multiple disabilities, who are also taking other medications against seizures.

In the case of liver damage clinical abnormalities mostly become apparent before any changes to laboratory values. Examples of such abnormalities are a loss of appetite, nausea, vomiting, abdominal pain, a dislike of foods which are normally liked, an aversion to valproic acid, tiredness, listlessness, impaired consciousnesses with confusion, apathy, restlessness and movement disorders, a feeling of physical weakness, an increase in the frequency/severity of the seizures, conspicuously frequent blue blotches/nosebleeds, fluid retention in the eyelids or legs and jaundice. In very rare cases there have also been reports of damage to the pancreas with similar symptoms.
The clinical monitoring of patients is therefore of greater importance than laboratory findings.

Measures for the early detection of liver damage:
a detailed clinical examination before the start of treatment (in particular with respect to metabolic disorders, diseases of the liver or pancreas and blood clotting disorders), as well as the laboratory chemical determination of the blood count with thrombocytes, bilirubin, SGOT, SGPT, gamma GT, lipase, alpha-amylase in the blood, blood sugar, total protein, Quick value, PTT, fibrinogen, factor VIII and associated factors. Patients should be closely monitored (particularly in the case of fever). Parents/caregivers should be informed of the possible signs of liver damage (see above) and be included in the monitoring process.

The parents and the attending physician should remain in close direct or telephone contact during the first six months of treatment:

The first telephone contact should take place two weeks after the start of treatment, with the first medical and laboratory chemical examination occurring after four weeks. Contacts with the doctor should then follow in weeks 8, 12, 16, 22, 28, 40 and 52. Telephone contacts in weeks 6, 10, 14, 19 and 34.

Irrespective of the above schedule, parents should inform the attending physician immediately of any clinical abnormalities.

Laboratory checks during doctor's visits:
In child patients without any abnormal symptoms: blood count with thrombocytes, SGOT and SGPT, during every second medical examination, also coagulation parameters. After 12 months of therapy without any abnormal symptoms only 2–3 medical examinations per year are necessary.

Consideration should be given to stopping therapy immediately in cases of:
an unexplained disturbance to the feeling of well-being, clinical symptoms of liver or pancreas damage or a tendency to bleeding, a more than two to three-fold increase in liver transaminases even without clinical symptoms (consider enzyme induction by any concomitant medication), a slight (one and a half to two-fold) increase in liver transaminases with a simultaneous acute febrile infection, pronounced disturbance of coagulation status.

In the case of **adolescents** (from around the age of 15 and up) and **adults**, monthly checks of clinical findings and laboratory values are recommended in the first six months, as well as before the start of therapy in all cases.

Children
Particular caution is required if Valpro TAD chrono 500 mg is taken by
- small children who are taking other medications to treat seizure disorders at the same time,
- children with multiple disabilities and adolescents with severe forms of seizures.

In the case of children and adolescents there have been occasional reports of dose-independent severe – and in individual cases fatal – damage to the liver, particularly during the simultaneous administration of other anti-epileptics. The impairment to liver function occurred mainly within the first six months of treatment, especially during the second and twelfth week of treatment, and was most frequently observed in infants and small children suffering from severe epileptic seizures, particularly if they also had brain damage, mental handicaps and/or a congenital metabolic disorder. In this group of patients Valpro TAD chrono 500 mg should only be used with particular caution and without simultaneous treatment with other medications against seizures.
For this reason children and adolescents should be closely monitored, particularly in the first six months of treatment.

Valpro TAD chrono 500 mg and acetylsalicylic acid (e.g. ASA, aspirin) for the treatment of high temperatures or pain should not be administered simultaneously to infants and small children in particular, as the tendency to bleeding may be increased (see also "Taking other medicines" and "4. Possible side effects").

Taking other medicines
Please tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, including medicines obtained without a prescription.

The effect and in some cases the side effects of Valpro TAD chrono 500 mg is/are increased by:
- felbamate (used in the treatment of seizure disorders), which increases the serum concentrations of free valproic acid (depending on the dose).
- cimetidine (used to treat stomach ulcers)
- erythromycin (used in the treatment of bacterial infections)
- acetylsalicylic acid (e.g. aspirin, ASA: used in the treatment of high temperatures and pain). Acetylsalicylic acid reduces the binding of valproic acid to blood protein. The simultaneous administration of Valpro TAD chrono 500 mg and acetylsalicylic acid should therefore be avoided, particularly in the case of infants and children, as the tendency to bleeding may have increased (see also the section on "Children" under "2. Before you take Valpro TAD chrono 500 mg").

The effect of Valpro TAD chrono 500 mg is weakened by
- other medications used in the treatment of seizures, such as phenobarbital, phenytoin and carbamazepine, due to the accelerated excretion of valproic acid
- primidone (used in the treatment of seizure disorders)
- mefloquine (for the treatment of malaria) and meropenem (an agent used to treat bacterial infections), which increase the breakdown of valproic acid and may also have a seizure-inducing effect
- panipenem (used to treat bacterial infections).

The effect of Valpro TAD chrono 500 mg may be increased or weakened by
- fluoxetine (used to treat depression) by increasing the valproic acid concentration of the serum. There have however been cases in which the valproic acid concentration of the serum was lowered.

Valpro TAD chrono 500 mg increases the effect and in some cases the side effects of medications used to treat seizures, such as
- phenobarbital (by increasing the serum concentrations of phenobarbital), which may be expressed by increased tiredness in children in particular,
- phenytoin (by reducing the binding of the phenytoin to plasma protein); this may increase the risk of side effects, particularly brain damage (see "Side effects"),
- primidone,
- carbamazepine,
- felbamate; serum levels of felbamate may double as a result of the simultaneous intake of valproic acid.
- lamotrigine (by inhibiting the degradation of lamotrigine). It is suspected that a combination of lamotrigine and Valpro TAD chrono 500 mg increases the risk of skin reactions.
- neuroleptics (medications taken to treat mental disorders)
- benzodiazepines (anxiolytic and tension-relieving agents) such as diazepam (as a result of an increase in the free diazepam, reduced degradation and reduced excretion) and lorazepam (especially as a result of reduced excretion)
- barbiturates (sedatives),
- MAO inhibitors (used in the treatment of depression and other medications used to treat depression)
- codeine (contained in cough medicines etc.)
- zidovudine (used in the treatment of HIV infections)
- anticoagulants (e.g. vitamin K antagonists), so that the tendency to bleeding may be increased.

In children the serum levels of phenytoin (another medication used to treat seizures) may be increased during the simultaneous administration of clonazepam (benzodiazepine; an anxiolytic and tension-relieving medication, as well as medication used to treat seizures) and valproic acid.

Particularly the combination of Valpro TAD chrono 500 mg and other medications used to treat seizures, depression and mental disorders may cause severe side effects. For this reason these medications must not be combined with Valpro TAD chrono 500 mg without consulting your doctor.

During simultaneous treatment with valproic acid-containing medications and clonazepam (used in the treatment of seizures), patients with absence-type seizures (a specific form of seizures emanating from both halves of the brain) in the past experienced an absence status (long-lasting comatose state).

One female patient with schizoaffective disorder (a mental disorder) undergoing simultaneous treatment with valproic acid, sertraline (an antidepressant) and risperidone (a neuroleptic) experienced catatonia (an unresponsive state which cannot be overcome by external stimuli).

Miscellaneous
- During the simultaneous administration of Valpro TAD chrono 500 mg, acetylsalicylic acid – e.g. ASA, aspirin (used to reduce pain and temperature) – may result in an increased tendency to bleeding (see also "Children" in the section "Take special care with Valpro TAD chrono 500 mg" and "4. Possible side effects").
- In diabetics an analysis of ketone bodies in the urine may provide incorrect results, as valproic acid itself is partially metabolised to ketone bodies.
- Other medications which place an extra burden on liver metabolism may increase the risk of the development of liver damage.
- The effect of contraceptive hormone preparations ("the pill") is not diminished by Valpro TAD chrono 500 mg.

Please note that the above information may also apply to medications taken until recently.

Taking Valpro TAD chrono 500 mg with food and drink
The consumption of alcohol may influence the effect of Valpro TAD chrono 500 mg and reinforce the side effects. You should therefore avoid drinking alcohol during treatment.

Pregnancy and breast-feeding
Pregnancy:
Before the start of treatment, women of a childbearing age should be advised by their doctor of the necessity of planning and monitoring any pregnancy that may occur.
The risk of the development of deformities of the spinal column and spinal cord is increased during treatment with Valpro TAD chrono 500 mg in early pregnancy.
Furthermore, there are other types of deformity whose risk of development is further increased during the simultaneous administration of other agents used in the treatment of seizure disorders.

For the early detection of possible damage to the child, diagnostic measures such as ultrasound and laboratory analyses in which alpha-fetoprotein is determined are recommended.

If there is a desire to have children or pregnancy has already occurred, Valpro TAD chrono 500 mg should be taken at the lowest seizure-controlling dose, particularly during early pregnancy (20th to 40th day after conception).
The daily dosage is taken over several small doses throughout the day, so that high peak concentrations of the active substance in the blood are avoided and the concentration of valproic acid in the blood over the course of the day is as even as possible.

Treatment with Valpro TAD chrono 500 mg during pregnancy should not be interrupted without the agreement of your doctor, as the sudden discontinuation of treatment or an uncontrolled reduction in the dose may result in epileptic seizures in the mother-to-be, which may damage you and/or the unborn child.

When a pregnancy is planned – and during the pregnancy itself – it is recommended that the folic acid levels should be checked and folic acid substitution carried out if necessary.

There have been reported cases of disruption to blood clotting (haemorrhagic syndrome) in newly born infants whose mothers were treated with valproate during pregnancy. This syndrome is attributable to a reduction of the fibrinogen in the blood. There have even been reports of fatalities resulting from the complete absence of fibrin. It is therefore advisable to examine the blood platelets, fibrinogen levels and coagulation factors of newborn infants and carry out coagulation tests.

Breast-feeding:
Valproic acid (the active substance contained in Valpro TAD chrono 500 mg) passes into the mother's milk. However, the quantities are small and do not generally represent a risk to the child, so that it is not usually necessary to wean the child.

Ask your doctor or pharmacist for advice before taking/using any medicine.

Driving and using machines
You must not take control of a motor vehicle or use machines without consulting your doctor first.
At the start of treatment with Valpro TAD chrono 500 mg, or if the dosage is increased or other medications which affect the central nervous system are taken simultaneously, the effects on the central nervous system, such as drowsiness or confusion, may affect your ability to react to such an extent that – irrespective of the effects of the underlying disorder being treated – your ability to drive a motor vehicle or use electric tools and machines is diminished. This applies in particular when taken in conjunction with alcohol.

3. HOW TO TAKE VALPRO TAD CHRONO 500 MG

Always take/use Valpro TAD chrono 500 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Unless otherwise prescribed by your doctor the standard dose is as follows:
The dosage should be determined and monitored from case to case by the doctor/specialist, with the aim being for the patient to be free of seizures at the lowest possible dosage, particularly during pregnancy.
Without prior consultation with your doctor you must not carry out any changes to the treatment or dosage in order to ensure that the success of the treatment is not placed in jeopardy.

It is recommended that the dosage be increased step-by-step (gradually) until the optimum effective dose is reached.

In patients where this is the only medication taken (monotherapy) the initial dose as a rule is 5 – 10 mg of valproic acid per kilogram of body weight, which should be increased every 4 – 7 days by approximately 5 mg of valproic acid per kilogram of body weight.

In some cases the full effect only becomes apparent after 4 – 6 weeks. Therefore the daily doses should not be increased too early to above-average levels.

In general the mean daily dose during long-term treatment is:
- 34.6 mg of sodium valproate per kilogram of body weight per day for children
- 28.8 mg of sodium valproate per kilogram of body weight per day for adolescents
- 23.1 mg of sodium valproate per kilogram of body weight per day for adults and elderly patients.

The following guideline daily doses are recommended accordingly: see dosage table

Dosage Table

Age	Body Weight (in kg)	Average Dose in mg/Day[1]	Quantity
Adults	approx. 60 and above	1200 – 2100	2 – 4 prolonged-release tablets containing 500 mg
Adolescents aged 14 and above	approx. 40 – 60	1000 – 1500	2 – 3 prolonged-release tablets containing 500 mg
Children:[2] 7 – 14 years	approx. 25 – 40	750 – 1200	1½ – 2 prolonged-release tablets containing 500 mg

[1] relative to sodium valproate

[2] **Note:**
For children aged six and under insufficient experience has been acquired of the use of prolonged-release pharmaceutical forms. For this age group the conventional pharmaceutical forms with a lower active substance content (e.g. solution, "juice" or tablets containing 150 mg) should be used.

If Valpro TAD chrono 500 mg is taken together with other medications used in the treatment of seizure disorders, or if it is intended to replace previous medication, the dose of the medication previously taken to treat the seizure disorders – especially phenobarbital – must be reduced immediately. If the previous medication is discontinued, this should be done gradually.

Other medications used in the treatment of seizure disorders accelerate the breakdown of valproic acid. If treatment with these medications is discontinued, the valproic acid concentration in the blood slowly rises, so that the valproic acid concentration must be checked over a period of 4 – 6 weeks. The daily dose of Valpro TAD chrono 500 mg should be reduced if necessary.

The concentration of valproic acid in the blood serum (determined before the initial daily dose) should not be higher than 100 µg/ml.

Special Patient Groups
In patients with impaired kidney function and protein deficiency in the blood, consideration should be given to an increase in free valproic acid in the serum and the dose reduced if necessary. However, the decisive factor in adjusting the dose should be the clinical picture and not the valproic acid levels in the serum.

The daily dose is distributed over 1 – 2 individual doses.

The following daily doses are recommended: see dosage table above

The required number of prolonged-release tablets is determined by the attending physician from case to case.
Please follow your doctor's instructions, as otherwise the medication cannot have the desired effect.

Previous treatment with conventional valproic acid-containing medications is replaced step-by-step with Valpro TAD chrono 500 mg until treatment can be continued with individual doses of Valpro TAD chrono 500 mg.
The changeover is carried out by the doctor on an individual basis.
The decisive factors in the selection of the strength of the dose and its tolerability are the serum levels and the clinical picture.

Method of Administration
Enteric-coated prolonged-release tablets to be taken orally

The enteric-coated prolonged-release tablets should be taken whole (not chewed) one hour before meals if possible (on an empty stomach in the morning) with plenty of fluid (e.g. 1 glass of water).

Length of Administration
As a rule, the treatment of seizure disorders is long-term.

A specialist (neurologist, neuropaediatrician) should decide on the adjustment, length of treatment, dosage and discontinuation of treatment with Valpro TAD chrono 500 mg from case to case, depending on the course of the individual disease.

In general, consideration should only be given to a reduction in the dose or the discontinuation of treatment with the medication after a period of two to three years has elapsed in which the patient has suffered no seizures.
The medication must be discontinued by reducing the dose step by step over a period of one to two years; children may be allowed to "grow out of" the dose per kilogram of body weight instead of adjusting the dose according to the child's age, although the EEG findings should not become worse.

Experience with the long-term use of Valpro TAD chrono 500 mg is limited, particularly with respect to children under the age of six years.

Occasionally the constituents of the prolonged-release tablets may be visible as a white residue in the patient's stools. This does not mean that the effect of the medication is reduced, as the active substance is completely dissolved out of the tablet (matrix) while it passes through the intestines.

Please speak to your doctor or pharmacist, if you have the impression that the effect of Valpro TAD chrono 500 mg is too strong or too weak.

If you take more Valpro TAD chrono 500 mg than you should
The undesirable effects referred to under "Side effects" may occur to a greater extent in the case of an overdose, e.g. an increased tendency to seizures and abnormal behaviour in both adults and children.
Whenever the medication is not taken in accordance with instructions a doctor should be informed immediately. If high doses have been taken, emergency measures should be initiated (admission to a hospital).
There is no known specific antidote. Treatment must therefore be restricted to general measures for removing the active substance from the organism and support for the vital functions.

If possible, vomiting should be induced or irrigation of the stomach and the administration of active charcoal should be carried out at an early stage (within 30 minutes of consumption). Intensive medical care may be required in individual cases.

If you forget to take Valpro TAD chrono 500 mg
Do not take a double dose to make up for a forgotten dose. You should then continue taking your medicine as prescribed.

If you stop taking Valpro TAD chrono 500 mg
Under no circumstances you must interrupt or prematurely stop treatment with Valpro TAD chrono 500 mg of your own accord. Please consult your doctor beforehand if you experience any intolerance or a change to your clinical picture. Otherwise you may jeopardise the success of your treatment and trigger renewed epileptic seizures.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valpro TAD chrono 500 mg can cause side effects, although not everybody gets them.

The following are used as a basis in the assessment of frequencies:

Very common: more than 1 in 10 patients	**Common:** fewer than 1 in 10, but more than 1 in 100 patients
Uncommon: fewer than 1 in 100 but more than 1 in 1000 patients	**Rare:** fewer than 1 in 1000, but more than 1 in 10,000 patients
Very rare: 1 or fewer than 10,000 patients, including individual cases	

It should be noted that at the beginning of treatment with Valpro TAD chrono 500 mg patients occasionally experience harmless, mostly temporary nausea, sometimes accompanied by vomiting and a lack of appetite; this abates of its own accord or if the dose is reduced.

Disturbances to blood coagulation and the blood-forming and lymphatic system
Common: A reduction in the number of blood platelets (thrombocytopenia) or white blood corpuscles (leucopenia), which often completely returns to normal if the medication is maintained, and always does if treatment with Valpro TAD chrono 500 mg is discontinued. Very rare: Impaired bone marrow function may result in further disturbances to constituents of the blood (lymphopenia, neutropenia, pancytopenia) or severe anaemia.
Valproic acid may inhibit blood clotting (the function of the blood platelets) and therefore cause prolonged bleeding times.
Uncommon: bleeding.

Disturbances to the body's own defence systems and hypersensitivity reactions
Rare: Reactions of the body's own defence systems towards its own connective tissue (lupus erythematosus) and inflammation of the blood vessels (vasculitis).
See also "Skin Disorders"

Metabolic Disorders
Very common: Isolated occurrences of a moderate increase in the ammonia serum level without changes to the liver function parameters, which does not necessitate stopping treatment.
Depending on the dose, an increase or loss of weight is commonly observed, as is an increase in or the loss of appetite.
Rare: A specific form of impaired kidney function (Fanconi syndrome), which returns to normal after the medication is discontinued.

Psychiatric Disorders
Cases of delusions have been observed.

Disorders of the Central Nervous System
Depending on the dose there are common reports of drowsiness, trembling or sensory disturbances in the form of pins and needles or numbness of the skin.
Uncommon: Headaches, muscle tension, unsteady gait, irritability, hyperactivity or confusion, particularly at the beginning of treatment.
Also uncommon: Cases of physical torpor while conscious (stupor) have been observed, some of which were associated with an increased frequency in the number of seizures and whose appearance diminished when the dose was reduced or the medication discontinued. The majority of these cases occurred as a result of combination therapy (particularly with phenobarbital) or after a rapid increase in the dose.
Uncommon: Shortly after the administration of valproic acid-containing medications an organic brain disease was observed irrespective of the dose, whose cause and developmental mechanism are unknown, and which may return to normal after discontinuation of the medication. Raised ammonia levels have been described in a few instances, and in the case of combination therapy with phenobarbital (another medication used to treat seizures) an increase in the phenobarbital level.
Rare: Chronic diseases of the brain (encephalopathy) with disruptions to brain functions, including mental performance, whose developmental mechanism has not been adequately determined, especially in association with high dosages or in combination therapy with other medications used in the treatment of seizures.
Individual cases of impaired brain performance, associated with shrinking of the brain tissue which returns to normal after treatment with Valpro TAD chrono 500 mg is stopped, have also been reported.
During **long-term therapy** with Valpro TAD chrono 500 mg together with other medications used to treat seizures, in particular phenytoin, there may be signs of brain damage (encephalopathy) accompanied by the increased occurrence of seizures, listlessness, cases of physical torpor while conscious (stupor), muscle weakness (muscular hypotonia), movement disorders (choreiform dyskinesias) and significant general changes to the EEG.

Hearing Disorders
Ringing in the ears has been observed.
There have been reports of temporary or permanent loss of hearing, although it cannot be stated with certainty that there is a causal connection with the administration of valproic acid-containing medications.

Disorders of the Gastrointestinal Tract
Uncommon: The excessive formation of saliva and diarrhoea have been observed, particularly at the start of treatment.
Uncommon: Particularly at the start of therapy, slight gastrointestinal disorders nausea, stomach pains) have been observed, which usually abated after a few days although treatment was continued.
Very rare: Reports of damage to the pancreas, in some cases with a fatal outcome.

Impaired Liver Function
Uncommon: **Independent of the dose,** severe (including fatal) disturbances to liver function. In children – particularly in the case of the simultaneous administration of other medications to treat seizures – the risk of liver damage is considerably higher (see " Take special care with Valpro TAD chrono 500 mg ").

Skin Disorders
Common: Depending on the dose temporary hair loss has been observed.
Rare: The administration of valproic acid-containing medications may result in reactions of the skin (erythema multiforme). There have also been individual reports of severe skin reactions (Stevens-Johnson Syndrome and toxic epidermal necrolysis or Lyell's Syndrome) (see also the section on "Taking other medicines").
See also "Disturbances to the body's own defence systems and hypersensitivity reactions"
Uncommon: Increased accumulation of fluid in the tissues (oedemas), particularly at the start of treatment.

Gynaecological and Reproduction Endocrinology Disorders
Rare: Irregular periods or the absence of menstruation;
Rare: Cystically enlarged ovaries and raised levels of the male sexual hormone testosterone.

Miscellaneous
Bedwetting has also been observed in children.

If you should observe one or more of the above side effects, please inform your doctor so that he or she can determine their severity and take any necessary measures.

Upon the occurrence of side effects which are **not dose-dependent**, it is necessary to discontinue the medication. If severe impairment to liver function or damage to the pancreas is suspected, your doctor must stop treatment with Valpro TAD chrono 500 mg immediately. As a precautionary measure other medications with the same metabolic breakdown, which can also have similar side effects, should also be discontinued. Nevertheless, in individual cases the clinical picture may progress.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VALPRO TAD CHRONO 500 MG?

Keep out of the reach and sight of children.

Do not use Valpro TAD chrono 500 mg after the expiry date which is stated on the carton and each blister pack after "EXP". The expiry date refers to the last day of that month.

The enteric-coated prolonged-release tablets must only be removed from the foil immediately before being taken.

6. FURTHER INFORMATION

What Valpro TAD chrono 500 mg contains
- The active substances are: valproic acid, sodium valproate
1 prolonged-release tablet contains 333.0 mg of sodium valproate (corresponding to 288.7 mg of valproic acid) and 145.0 mg of valproic acid.

- The other ingredients are:
Hypromellose, acesulfame potassium, colloidal hydrated silica, sodium dodecyl sulphate, dibutyl decanedioate, basic butyl methacrylate copolymer (Ph. Eur.), magnesium stearate (Ph. Eur.), titanium dioxide (E 171)

What Valpro TAD chrono 500 mg looks like and contents of the pack
Valpro TAD chrono 500 mg is a capsule-shaped, white prolonged-release tablet with a break score on both sides.

Packs of 100 prolonged-release tablets.

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