Convulex® 100 mg/ml - Solution for Injection

Active ingredient: Sodium valproate

Reg. no. (Austria): 1-25002

Composition:

1 ampoule with 5 ml of solution for injection contains 500 mg sodium valproate (corresponding to 433.9 mg valproic acid).

Excipients: Disodium hydrogen phosphate dodecahydrate, sodium hydroxide, water for injection.

Dosage form:

Solution for injection, concentrate for solution for infusion

Pack size:

5 ampoules (colourless glass, glass type I) of 5 ml each.

Characteristics and action:

Valproic acid is an antiepileptic which does not show any structural similarities to other anticonvulsant substances. Valproic acid has anticonvulsant efficacy in man. It is assumed that valproic acid acts by potentiating GABA-mediated inhibition through a pre-synaptic influence on GABA metabolism and/or by exerting a direct post-synaptic effect on the ion channels of the neuronal membrane.

Valproic acid is poorly soluble in water (1:800), but easily soluble in water when bound to the sodium salt (1:0.4).

Marketing authorisation holder and manufacturer:

Gerot Pharmazeutika Ges.m.b.H., Vienna

Therapeutic indications:

For the treatment of epileptic seizures, if oral administration of valproic acid is temporarily not possible.

Effective in:

- generalised seizures in the form of absence seizures, myoclonic seizures, tonic-clonic seizures, atonic seizures and mixed seizure types,
- focal seizures in the form of simple and complex seizures, secondarily generalised seizures, and specific syndromes (West syndrome, Lennox-Gastaut syndrome).

In infants and toddlers sodium valproate is the drug of choice only in exceptional cases; Convulex Solution for Injection should be used with special caution, only after careful weighing of benefits and risks, and preferably in monotherapy.

Contraindications:

Convulex Solution for Injection must not be used in case of:

- hypersensitivity to sodium valproate or any other constituents of the medicinal product,
- severe liver diseases in the patient's own history or that of relatives, particularly if drug-related,
- manifest severe impairment of hepatic or pancreatic function,
- liver function disturbances resulting in death in siblings treated with valproic acid,
- hepatic porphyria,
- blood coagulation disturbances,
- renal dysfunction,
- insulin-dependent diabetes mellitus.

Sodium valproate should be used with special caution in case of:

- infants requiring concomitant treatment with several antiepileptics,
- children and adolescents with multiple accompanying disorders and severe seizure forms,
- bone marrow damage,
- congenital enzyme deficiencies,
- hypoproteinaemia,
- systemic lupus erythematosus.

Pregnancy and lactation:

Pregnancy:

During pregnancy a treatment with valproate should not be interrupted without medical advice, as sudden discontinuation or uncontrolled dose reduction may induce epileptic seizures in the pregnant woman which may harm her and/or the unborn child.

Women of child-bearing age should be informed before the beginning of treatment about the necessity of planning and monitoring a pregnancy. Folate supplementation should be started in early pregnancy, or possibly already when planning pregnancy or from the time of conception. The risk of malformation is 2 to 3 times higher (approximately 6–9%) in children of epileptic mothers receiving antiepileptic therapy than in the general population (approximately 3%). The risk of malformation increases when multiple antiepileptic drug therapy is administered.

Before planning a pregnancy, the need for antiepileptic treatment should be reassessed. If sodium valproate is considered essential, it should be administered at the minimum effective dose level and as a sole agent throughout the pregnancy and particularly during the first 3 months of pregnancy. As it is very likely that malformations are caused by peak serum concentrations of the substance, the total daily dose should be administered in several smaller doses spread out over the day in all women desiring to become pregnant, but in any case between days 20 and 40 after conception. In addition, serum concentrations should be monitored regularly.

After remaining on a relatively constant level during the first and second trimesters of pregnancy, concentrations of free valproic acid were seen to rise during the 3rd trimester to up to their triple value at childbirth. Withdrawal symptoms in babies born to mothers treated

Effects of other substances on sodium valproate:

Enzyme-inducing antiepileptics such as phenobarbital, primidone, phenytoin and carbamazepine lead to an increase in valproic acid elimination, a reduction of its plasma levels and thus a decrease in effect.

Felbamate leads to a dose-dependent, linear increase (18%) in the serum concentration of free valproic acid.

Mefloquine enhances the metabolisation of valproic acid and has a convulsant effect. Its concomitant administration may therefore induce epileptic seizures.

Due to inhibition of the hepatic metabolism, valproic acid plasma levels may be increased when cimetidine and erythromycin are co-administered.

The concomitant administration of fluoxetine may also lead to an increase in valproic acid serum levels; however, there have also been reports of a decreasing effect.

When Convulex Solution for Injection and panipenem or meropenem were co-administered, serum levels of valproic acid were lowered. Occasionally this decrease was accompanied by the occurrence of seizures. If panipenem or meropenem are given concomitantly, valproic acid levels should therefore be monitored carefully.

Substances highly bound to plasma proteins, such as acetylsalicylic acid, may displace sodium valproate from its plasma protein binding sites and thus increase the free fraction of valproic acid in plasma. The concomitant administration of sodium valproate and acetylsalicylic acid at antipyretic/analgesic doses should therefore be avoided; this applies particularly to infants and toddlers.

Effects of sodium valproate on other substances:

The increase in phenobarbital concentrations caused by sodium valproate is of special clinical significance as it may manifest in the form of pronounced sedation, particularly in children. If this effect occurs, the dose of phenobarbital or primidone must be reduced (primidone is partly metabolised to phenobarbital). Careful monitoring is therefore recommended especially during the first 15 days of combined therapy.

If medicinal products containing valproic acid are added to an existing therapy with phenytoin, or if their dosage is increased, the amount of free phenytoin (concentration of the active, non protein-bound fraction) may be increased, while total phenytoin serum levels remain unchanged. As a consequence, the risk of side effects (particularly a damaging effect on the brain) may be enhanced (see also „Undesirable effects").

For the combined therapy with carbamazepine and valproate, symptoms possibly resulting from a potentiation of the toxic effect of carbamazepine by valproic acid have been described. Clinical monitoring is therefore indicated especially at the beginning of such a treatment; if necessary, doses should be adjusted.

Sodium valproate leads to a reduced clearance of lamotrigine and thus to a marked prolongation of its half-life. The dosage of lamotrigine should therefore be adapted, if appropriate. An increased risk of skin reactions due to combined use of lamotrigine and drugs containing valproic acid has been suspected on the basis of individual reports of serious skin reactions occurring within 6 weeks of the start of combination treatment and partly subsiding upon discontinuation of the medication, or else upon adequate treatment of the symptoms.

Valproic acid may increase the serum levels of felbamate by approximately 50%.

When used in combination with benzodiazepines, barbiturates, neuroleptics, MAO inhibitors and antidepressants, valproate may enhance the CNS-depressant effect of these drugs. If any such combinations are used, patients should be carefully monitored and dosages should be adjusted as appropriate.

The metabolism and extent of protein binding of other substances, such as codeine, may also be influenced.

Valproic acid possibly increases zidovudine serum concentrations, which may lead to increased zidovudine toxicity.

Concomitant administration of sodium valproate and anticoagulants or acetylsalicylic acid may increase the bleeding tendency. During their combined use coagulation parameters should therefore be checked regularly.

Other interactions:

As valproic acid is partly metabolised to ketone bodies, one should bear in mind the possibility of a false-positive result of a ketone body excretion test in diabetic patients in whom ketoacidosis is suspected.

As valproate does not have an enzyme-inducing effect, the action of hormonal contraceptives is not diminished by valproate.

It cannot be ruled out that potentially hepatotoxic drugs as well as alcohol may potentiate the toxic effects of valproic acid on the liver.

Special warnings:

Hepatic and pancreatic damage:

Rarely severe hepatic damage and very rarely pancreatic damage have been observed. Both conditions may take a lethal course. The risk of a fatal outcome is increased if hepatitis and pancreatitis occur simultaneously.

Patients predominantly affected are children under 15 years of age, but most frequently infants and toddlers under 3 years who suffer from severe epileptic seizure disorders. The risk is particularly increased if they receive combined treatment with several antiepilepsy drugs or if they also suffer from brain damage, mental retardation and/or congenital metabolic disorders. In this group of patients, valproic acid should be used with special caution and in monotherapy. Experience has indicated that the incidence of these

with valproate have been described.
The risk of development of a meningomyelocele is increased in case of exposure during an early phase (first trimester) of pregnancy (incidence: 1–2% of exposed patients). In addition, other malformations, including a foetal antiepileptics syndrome, may occur, the risk rising with concomitant use of other antiepileptics.
There have been reports of blood coagulation disorders (haemorrhagic syndrome) in neonates whose mothers were treated with valproate during pregnancy. This syndrome is related to hypofibrinogenaemia. Even some fatalities due to complete absence of fibrin have been reported. Hypofibrinogenaemia may occur in association with a drop in coagulation factors. However, one must differentiate between this syndrome and a decrease in vitamin K dependent coagulation factors, which may be caused by phenobarbital and enzyme-inducing agents.
Platelet count, fibrinogen level and coagulation factors should therefore be investigated in neonates and coagulation tests should be done.
Prenatal screening methods for early detection of abnormalities (ultrasound, alpha-foetoprotein measurement) are recommended.
Valproate passes the placenta and reaches higher concentrations in foetal serum than in maternal serum.

Lactation:
Valproic acid is excreted into breast milk. At steady state, the concentration in breast milk is up to 10% of that in the serum. In general, this does not pose a risk to the infant so that it is usually not necessary to discontinue breast-feeding.

Special precautions for use:
Caution: Use of this drug may affect reactivity and your ability to drive. At the beginning of sodium valproate therapy, at higher dose levels and/or in combination with medicinal products acting on the central nervous system, CNS-related effects such as somnolence or confusion may affect reactivity to such an extent that – independent of the effects of the underlying disease – the patient's ability to actively participate in road traffic or to operate machinery may be impaired. Such effects may be even enhanced in connection with concomitant alcohol consumption.
The doctor should be informed immediately of the onset of pregnancy.
Always keep this medicinal product out of the reach and sight of children.

Interactions:
Especially at the beginning of an antiepileptic therapy combining Convulex Solution for Injection with other anticonvulsants, monitoring of plasma levels is recommended so that the dosage of the individual antiepileptics can be adjusted as required.

disorders considerably decreases above this age group (notably above 10 years of age).
In the majority of cases, liver damage was observed within the first 6 months of treatment, particularly between weeks 2 and 12, and mostly when other antiepileptics were co-administered.
Serious or fatal liver damage may be preceded by non-specific symptoms, such as recurrence or increase in frequency or severity of seizures, physical malaise, loss of appetite, dislike of habitual food, aversion to valproate, vomiting, upper abdominal pain, unusually frequent bruising or nose-bleed, oedemas in certain areas of the body or generalised oedema, lethargy. Patients (and particularly infants and toddlers) should be closely monitored for any of these symptoms.

Measures for early detection of hepatic damage:
Before the beginning of therapy, the medical history of the patient and his/her family has to be recorded in detail and an extensive clinical examination has to be carried out, with a special focus on metabolic, hepatic or pancreatic disorders and coagulation disturbances. Laboratory tests of hepatic function (SGOT, SGPT, gamma-GT, bilirubin, total protein), coagulation parameters (prothrombin time, partial prothrombin time, fibrinogen), blood count (including thrombocyte count), lipase, serum a-amylase and blood glucose should be done before the start of therapy as well as in children after 1, 3, 5, 7 and 9 weeks of treatment and then at 4-week intervals through-out the first 6 months of therapy.
In adolescents (approximately from the age of 15 years) and adults, clinical and laboratory parameters should be examined before the start of therapy, and then at monthly intervals throughout the first half year of treatment. In patients who show no clinical symptoms or signs, but have laboratory values above the normal range at the end of 4 treatment weeks, the further course should be checked 3 times at maximum intervals of 2 weeks, then once per month until the end of 6 months of therapy.
Especially patients developing a fever should be closely monitored. Parents and other persons looking after the patient should be informed about the possible symptoms of liver damage; they should take an active part in the monitoring process and should be advised to immediately inform the treating physician of any unusual signs.
After a therapy duration of 12 months with no abnormal occurrences, 2–3 medical check-ups per year are usually sufficient.
Immediate discontinuation of therapy should be considered in cases of:
unexplained general malaise, clinical symptoms of hepatic or pancreatic impairment or increased bleeding tendency, more than 2- to 3-fold increase in liver transaminases even in the absence of clinical signs (the possibility of enzyme induction by concomitant medication should be borne in mind), mild (1½–to 2-fold) increase in

liver transaminases accompanied by acute symptoms of flu with fever, marked disturbance of coagulation parameters (decrease in fibrinogen and coagulation factors).
If a severe disturbance of liver function is suspected, other substances which might lead to similar side effects due to the same metabolic pattern (e.g. salicylates) should also be discontinued as a precautionary measure. In individual cases the clinical picture may continue to deteriorate none-theless.

Other precautions:
During treatment with preparations containing valproic acid, serum ammonia levels may rise (hyperammonaemia). If symptoms such as apathy, somnolence, vomiting or hypotension occur or if the frequency of seizures increases, serum levels of ammonia and valproic acid should therefore be determined; if necessary, the drug dosage should be reduced.
When a pre-existing urea cycle enzymatic deficiency is suspected, careful investigations of any metabolic abnormalities should be performed prior to valproate treatment to prevent the occurrence of hyperammonaemia.
It should be noted that – like with other antiepileptics – transient increases of transaminases without clinical symptoms may occur at the beginning of a therapy with valproic acid.
In rare cases slight, mostly transient nausea, sometimes accompanied by vomiting and anorexia, may occur, but usually resolves either without any measures being taken or after dose reduction.
If side effects are observed that are not dose-related, Convulex Solution for Injection should be discontinued.
Prior to surgical interventions and if spontaneous bleeding or haematomas occur, coagulation parameters should be examined.
Frequent controls of prothrombin time are recommended, if vitamin K antagonists are administered concomitantly.
Patients with a history of bone marrow damage must be closely monitored.

Incompatibilities:
If other drugs are co-administered via the intravenous route, Convulex Solution for Injection should be given via a separate line, as incompatibilities cannot be ruled out.

Dosage and administration:

Dosage:
Daily doses should be chosen and individually adapted according to age, body weight, and individual sensitivity to valproate. The aim, especially also during pregnancy, should be optimal seizure control at minimal dosage.
As there is no therapeutically relevant correlation between daily dose, serum concentration and therapeutic effect, optimal dosage has to be determined on the basis of clinical response. If adequate seizure control cannot be achieved or if side effects are suspected, measurement of valproate plasma levels may be considered in addition to clinical monitoring. The effective range usually lies between 40 and 100 mg/litre (300–700 µmol/l).

In general, the following dosage recommendations apply:
If administered by slow intravenous injection, the recommended dose is between 5 and 10 mg sodium valproate per kg body weight. In adult patients, this corresponds to approximately 500 mg sodium valproate or 1 ampoule for a patient weighing 65 kg.
If given as an infusion, the recommended dose is 0.5–1 mg sodium valproate per kg body weight per hour.
Use in patients already on a treatment regimen with oral valproic acid:
When switching patients from oral to i.v. administration, this can be done on a 1:1 dose ratio; the solution for injection of Convulex should be administered 12 hours after the last oral dose, either in the form of single injections or as an infusion.
In cases where it is necessary to rapidly reach and maintain high plasma concentrations, the following approach is recommended: intravenous injection of 15 mg of sodium valproate per kg body weight within 5 minutes. 30 minutes later start of an infusion of 1 mg/kg BW/h under constant monitoring until a plasma concentration of about 75 µg/ml is reached. For optimal adaptation of therapy to individual requirements, dosage should be adjusted according to the clinical state of the patient.
If repeated injections or a continuous infusion of Convulex Solution for Injection are administered, a maximum daily dose of 2500 mg sodium valproate must not be exceeded.
In infants older than 2 months and children the dose level previously given orally (usually in the range of 20–30 mg sodium valproate/kg BW/day) can usually be maintained. The intravenous injection or infusion is administered at a dosage of approximately 0.8–1.35 mg/kg BW/hour.
In general, average daily doses are in the range of
- 20 mg sodium valproate/kg body weight in adults and elderly patients,
- 25 mg sodium valproate/kg body weight in adolescents,
- 30 mg sodium valproate/kg body weight in children.

Infusion rate:
On the basis of 1 ampoule (= 500 mg sodium valproate) in 500 ml solution for infusion, the infusion rate is 1 ml of solution for infusion/kg BW/h.
When giving a medicinal product containing valproic acid in combination with another antiepileptic medication, the dosage of the antiepileptics used so far has to be reduced immediately, particularly in the case of phenobarbital. If the previous medication is to be

At therapeutic plasma levels (range: 40–100 µg/ml), sodium valproate shows relatively low toxicity. Very rare cases of acute intoxication with valproic acid have been observed in adults and children at serum levels exceeding 100 µg/ml. Isolated cases of acute or chronic overdosage resulting in fatalities are known from literature.

a) Symptoms of intoxication:
Characteristic symptoms include states of confusion, sedation (sometimes progressing to coma), myasthenia, hyporeflexia or areflexia. Individual cases of hypotension, miosis, cardiovascular and respiratory irregularities, cerebral oedema and intracranial hypertension, metabolic acidosis and hypernatraemia were observed.
High serum levels cause neurological disturbances, such as increased seizure frequency or behavioural changes, in adults and children.

b) Therapy of intoxication:
No specific antidote is known. Therapy therefore has to consist in general measures for eliminating the active substance from the organism and supporting vital functions.
If the intoxication results from oral administration, early measures such as induced vomiting (within 30 minutes) or gastric lavage (up to 10–12 hours after ingestion) as well as administration of activated charcoal and close monitoring under intensive care conditions are indicated.
Furthermore, haemodialysis and forced diuresis may be effective. Peritoneal dialysis seems to be less useful. There is insufficient experience with regard to the effectiveness of charcoal haemoperfusion and of complete plasma substitution or transfusion. For intoxications of mild to moderate severity, intensive clinical care without specific detoxification procedures, but with monitoring of plasma concentrations is therefore recommended (especially in children). The intravenous administration of naloxone against clouding of consciousness has been reported as being effective in some cases.

Undesirable effects:
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Gastrointestinal tract:
Occasionally dose-related increase or decrease in weight, increased appetite or anorexia, taste perversion. Rarely hypersalivation, diarrhoea, vomiting, singultus. In rare cases gastrointestinal disturbances such as nausea or gastric pain were observed for a few days especially at the beginning of treatment, but did not necessitate discontinuation of therapy. Rarely dose-independent serious liver function disturbances (sometimes taking a lethal course) have occurred. The risk of developing liver damage is significantly increased in children, especially if they receive multiple antiepileptic treatment.
During treatment patients should be monitored especially for the following symptoms which may be signs of hepatic or pancreatic damage: decrease in antiepileptic effect characterised by recurrence or increased frequency of epileptic seizures; persisting symptoms such as weakness, apathy, anorexia, lethargy, nausea and repeated vomiting or unclear abdominal pain, increased oedemas affecting the whole body or certain areas, disturbed consciousness with confusion, restlessness and motor disturbances.
Individual cases of pancreatic damage, preceded by symptoms similar to the ones described above and sometimes resulting in fatalities, have been reported.
Infants and toddlers should be monitored very carefully for these symptoms. If symptoms like the ones described are persistent or severe, detailed medical examination should be accompanied by the appropriate laboratory tests.

Central nervous system:
Occasionally headaches, somnolence, drowsiness, tremor and paraesthesia have occurred. Rarely, spasticity and disturbed coordination of movements, irritability, hyperactivity, hallucinations and tinnitus have been reported. Reversible or irreversible hearing loss has been reported, but a causal relationship with drugs containing valproic acid has not been established.
Confusion and stupor, which may partly be associated with an increase in seizure frequency and may lead to encephalopathy, also occur rarely. They have been reported predominantly with very rapid dose increases of sodium valproate and with antiepileptic combination therapies (esp. with phenobarbital) and are usually reversible on dose reduction or discontinuation of therapy.
During long-term therapy with medicinal products containing valproic acid in combination with other antiepileptics, particularly phenytoin, symptoms and signs of brain damage (encephalopathy) may develop: increase in seizures, lack of drive, stupor, myasthenia (muscular hypotonia), motor disturbances (choreiform dyskinesia) and severe general EEG changes.
Individual cases of dementia, together with cerebral atrophy, which were reversible upon discontinuation of the medication, have also been reported. Furthermore, the occurrence of a reversible Parkinson syndrome under valproic acid has been reported.

Haematologic:
Rarely bleeding has occurred. Occasionally thrombocytopenia (particularly in children) or leukopenia occur, which often resolve even when the medication is continued unchanged, but which are always completely reversible when valproic acid is discontinued. In individual cases, impaired bone marrow function may lead to

discontinued, this should be done gradually.
Since the enzyme-inducing effect of other antiepileptics is reversible, valproic acid serum levels should be checked about 4–6 weeks after stopping an antiepileptic drug of this kind and daily doses should be reduced if necessary. The serum concentration (measured before the first administration of the day) should not exceed 100 µg valproic acid/ml.
In patients with renal insufficiency and hypoproteinaemia, the increase in free valproic acid in the serum should be taken into account; if required, doses may have to be reduced.
Method and duration of administration:
For intravenous injection.
Convulex Solution for Injection should be either injected slowly (over 3-5 minutes) strictly via the intravenous route, or be administered as an infusion (continuously or in repeated doses).
Intra-arterial and peri-venous application have to be avoided due to the risk of tissue damage.
Use only clear and colourless to slightly yellow solution.
Solutions for infusion containing Convulex Solution for Injection should be used within 24 hours of reconstitution; until use they have to be stored at 2–8° C. Any unused portion of the solution has to be discarded.
The following solutions may be used for preparing the infusion:
– isotonic sodium chloride solution,
– glucose solution 5%,
– lactated Ringer's solution.
If other drugs are co-administered via the intravenous route, Convulex Solution for Injection should be given via a separate line.
Convulex Solution for Injection should be replaced by an oral dosage form as soon as the patient's state of health permits. As a rule, oral administration is started 12 hours after the end of the infusion.
Antiepileptic treatment is generally a long term therapy. Initiation of therapy, duration of treatment and discontinuation of medicinal products containing valproic acid should be decided on an individual basis by a neurologist or a specialist in paediatric neurology. Usually, dose reduction and discontinuation of the medication should be considered only when patients have been seizure-free for at least 2–3 years. Discontinuation has to be done by very gradual dose reductions over one to two years; during this period, EEG findings should not deteriorate. When reducing the dosage in children, it is possible to take into account an age-related shift in the dose per kg body weight ratio.

Overdose
When assessing a case of intoxication, the possibility of added toxicity due to multiple drug intake, e.g. with a suicidal intention, should be considered.

lymphopenia, neutropenia, pancytopenia or anaemia.
Sodium valproate may lower the concentration of fibrinogen and/or coagulation factor VIII and inhibit the secondary phase of platelet aggregation, thus causing a prolonged bleeding time.
Isolated decreases in fibrinogen concentration, mostly without any clinical symptoms and predominantly occurring with high dose levels, have been reported.
Skin and appendices:
Occasionally local reactions at the injection site, transient hair loss, and rarely inflammations at the injection site as well as peripheral oedema occur.
Inadvertent intraarterial or perivenous application may give rise to tissue damage.
In individual cases, the administration of medicinal products containing valproic acid has led to skin reactions (erythema multiforme) and changes of immunological defence mechanisms (vasculitis, lupus erythematosus). Allergic reactions have been reported. In addition, a few exceptional cases of serious skin reactions (Stevens-Johnson's syndrome, toxic epidermal necrolysis or Lyell's syndrome) have been reported.
Changes of laboratory test values:
Frequently isolated and moderate hyperammonaemia without abnormal liver test values or manifestation of clinical symptoms and not necessitating discontinuation of therapy may occur.
There have been individual reports of elevated testosterone levels and polycystic ovaries.
Furthermore, occurrence of amenorrhoea and irregular menstrual cycles have been reported.
There have been isolated literature reports of a Fanconi´s syndrome (metabolic acidosis, phosphaturia, amino aciduria, glycosuria) reversible upon discontinuation of valproate therapy, but the underlying mechanisms are as yet unclear.
Other:
Rarely, non-specific pain and enuresis in children have been seen.
With Convulex Solution for Injection, nausea and drowsiness may occasionally occur a few minutes after administration, but spontaneously resolve within a few minutes.

Expiry date and storage advice:
Do not use after the expiry date indicated on the label.
Reconstituted solutions for infusion containing Convulex should be used up within 24 hours and have to be stored at 2–8° C until use.

Latest update:
June 2003

Please contact your physician or pharmacist for any further information about Convulex Solution for Injection.