COMPOSITION
1 ml (= 30 drops) contains 300mg sodium valproate.
Excipient: Purified water.

PHARMACEUTICAL FORM
Oral drops

NATURE AND CONTENTS OF CONTAINER
Copper bottle containing 40 ml.

THERAPEUTIC INDICATIONS

Epilepsy:
- Primary generalized seizures and generalized epilepsies
  Seizure types: absences, myoclonic seizures, primary generalized tonic-clonic seizures (including infantile febrile convulsions), infantile spasms
  Epileptic syndromes: absence epilepsy, juvenile myoclonic epilepsy (Janz syndrome), photosensitive epilepsies, epilepsy with generalized tonic-clonic seizures on awakening. Lennox-Gastaut syndrome, West syndrome
- Focal (partial: seizures and epilepsies, with and without secondary generalization.

Affective psychoses: (adult patients only):
Treatment of acute manic episodes associated with manic-depressive disorder.

Migraine (adult patients only):
Prophylaxis of migraine headaches, if other drugs have not shown the desired effect.

POSOLOGY AND METHOD OF ADMINISTRATION

Epilepsy:
The recommends initial dose is 15 mg/kg daily, to be increased by 5-10 mg/kg at one week intervals until the patient is seizure-free.

General dosage guideline: 30 mg/kg body weight per day

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Average daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 -15kg</td>
<td>150 - 450mg (15-45 drops)</td>
</tr>
<tr>
<td>10-20kg</td>
<td>300- 600mg (30-60 drops)</td>
</tr>
<tr>
<td>20-30 kg</td>
<td>600- 900 mg (60-90 drops)</td>
</tr>
<tr>
<td>30-50 kg</td>
<td>900-1500mg (90-150 drops)</td>
</tr>
<tr>
<td>kg or more</td>
<td>3 drops per kg body weight</td>
</tr>
</tbody>
</table>

As a rule, the daily, dosage should be divided into several doses. During monotherapy with valproic acid, the total daily dose can also be administered once a day in the evening (up to a maximum dose of 10 mg/kg body weight/day).
Monitoring of blood levels may be indicated (e.g. for checking compliance, determining potential intoxication: see 5.2 Pharmacokinetics).

In pre-treated patients, the previous anticonvulsive medication is to be reduced gradually.

Affective psychoses: (Adult patients only)
The recommended initial dosage is 600-900 mg (60-90 drops) daily, divided into several doses. Highly agitated patients may be treated with up to 1500 mg/day.
Gradual dose increases should then be effected at intervals of 2 to 4 days and accompanied by monitoring of plasma levels (usual therapeutic range: between 50 and 125 mg/l) until clinical improvement or side effects are observed.

**Migraine:** (Adult patients only)

Starting at 300 mg (30 drops) per day in divided doses, the daily dosage is slowly increased until the desired therapeutic effect is achieved or side effects occur. Most patients can be effectively treated with 600-900 mg (60-90 drops) per day. For higher dosage requirements, Convulex 500 mg capsules are available.

**Method of administration:**
The drops should be taken in half a glass of sweetened water.
For the dropper to work properly, the bottle should be held in a vertical position (it necessary, lightly tap the bottom of the bottle).

**CONTRA-INDICATIONS**
- Hypersensitivity to valproic acid, disturbances of hepatic or pancreatic function;
- **Special caution** is required in the following cases:
  - history of liver or pancreas diseases or bone marrow damage
  - hemorrhagic diathesis (tendency to bleeding)
  - impaired kidney function
  - congenital enzyme defects
  - severe epileptic seizure types
  - mentally retarded children
  - organic cerebral (brain) lesions
  - children younger than 3 years (as they are especially predisposed for liver damage; cf. Undesirable effects).

**SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**

Liver function tests, coagulation parameters (bleeding lime, Quick’s lest, plasma fibrinogen, thrombocyte count, platelet aggregation, thrombelastogram) and determination of serum amylase and lipase should be performed before the start of treatment as well as with every dose increase and at 2-monthly intervals during treatment.

Treatment must be stopped immediately, if one of the following occurs:
- hypofibrinogenemia, coagulation disorders, increase in transaminases to their triple value, increase in alkaline phosphatase or serum bilirubin, symptoms or signs of toxic hepatitis (pathological laboratory values together with clinical symptoms).
- If only transaminases are slightly increased, dosage should be reduced and liver function as well as coagulation parameters should be monitored.

Pancreatic function (amylase, lipase) should be monitored before initiating therapy and repeatedly during treatment with valproic acid, and especially if unclear abdominal pain, symptoms of organic damage or hemorrhagic disorders (bleeding anomalies) occur. At the first indication of pancreatitis (abnormal laboratory values accompanied by clinical symptoms) treatment is to be stopped immediately.

Renal function and serum ammonia levels should also be monitored at regular intervals. Due to a possible increase in bleeding tendency, caution is required in connection with surgical or dental interventions.

Sudden discontinuation of vaiprolc acid therapy may lead to an Increase in seizure frequency.
INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION
Valproic acid displaces phenytoin, phenobarbital and diazepam from plasma protein binding, which leads to an increase in the quantity of free substance. The metabolism of diazepam is inhibited by valproic acid. Serum levels of primidone are increased. The effect of ethosuxi-mide is potentiated. Phenytoin, phenobarbital and primidone lead to increased clearance and reduced plasma levels of valproio acid. Concomitant administration of carbamazepine may either increase or decrease the plasma levels of valproic acid. In rare cases concomitant administration of clonazepam may induce absences. In case of combination therapy with other anticonvulsants, careful determination of blood levels (drug monitoring) is therefore essential. Concomitant use of felbamate leads to increased plasma levels of vapiroic acid. Concomitant administration of lamotrigine increases the elimination half-life of that substance.
Vaiproic acid potentiates the CNS depressant effect of certain drugs (such as barbiturates, primidone, neuroleptics and antidepressants) and of alcohol. The action of platelet aggregation inhibitors (acetylsalicylic acid), anticoagulants of the coumarin type and heparin is potentiated. According to several studies, salicylates replace valproic acid from its serum albumin binding sites and affect its metabolism, which may result in toxic concentrations of valproic acid (this is clinically relevant especially in children). Concomitant administration of hepatotoxic drugs may potentiate the possible adverse effects of valproic acid on the liver. No interaction with oral contraceptives has been reported.
Effects of valproic acid on laboratory parameters:
Valproic acid is partially eliminated in the urine as a keto-metabolite which may lead to a false positive result of the urine ketone test in diabetic patients. Depending on the plasma concentration, valproic acid may lead to a displacement of thyroid hormones from their protein binding sites and to their more rapid metabolism, so that thyroid function tests may wrongly lead to a suspicion of hypothyroidism.

PREGNANCY AND LACTATION
Animal studies have demonstrated that valproic acid may have a teratogenic effect. In humans, neural tube defects (spina bifida) have been observed. Therefore the minimum effective dosage of valproic acid should be given during pregnancy. Combination with other antiepileptic drugs should be avoided. During the first three months of pregnancy, valproic acid therapy should not be initiated. It the pregnant woman has been receiving treatment with valproic acid, the drug should not be stopped abruptly due to the risk of increased seizure frequency or induction of status epilepticus which could be life-threatening for both mother and child. Valproic acid levels should be monitored (therapeutic range).
In indications other than epilepsy valproic acid should be used during pregnancy only after extremely careful weighing of benefits and risks. Ablactation is recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Reactivity may be impaired especially in combination with alcohol and at the beginning of therapy, so that the patients’ ability to drive or operate machinery may be affected.
The consumption of alcohol should be avoided.

**UNDESIRABLE EFFECTS**

In general, Convulex capsules are well tolerated. Side effects are only seen in rare cases and are seen most frequently when plasma levels exceed IOU mg/l or whenConvulex is used in combination therapy. The most commonly reported side-effects relate to the gastrointestinal system. Nausea, vomiting and anorexia (loss of appetite) mainly occur at the beginning of therapy, but usually disappear with dose adaptation and administration together with or after meals. Increased appetite, weight gain, gastric pain or cramps, diarrhoea and constipation have also been reported.

Rare side-effects include sedation, vertigo (dizziness), headache, depressive state, aggression, involuntary movements, hyperactivity, tonic spasms, impaired coordination (ataxia, asterixis, dysarthria), trembling, nystagmus (twitching of the eye), and diplopia (double vision). In isolated cases, states of contusion, disturbed consciousness (stupor, coma) were observed a few days after therapeutic plasma levels were reached; in these cases, a paradoxical effect in patients with a history of psychic disorders was suspected. Various blood disturbances have been reported with valproic acid (including thrombocytopenia, inhibition of platelet aggregation, neutropenia, lymphocytosis, hypofibrinogenemia, in extremely rare cases also anemia and bone marrow depression). Serum anomalies (hyperammonaemia, increase in serum glycin levels and decrease in carnitine levels) have also been reported.

Allergic skin reactions occur very rarely. Individual cases of petechial bleeding (minute red spots in the skin), tendency to develop haematoma (bruises), end transient heir loss have been seen. The occurrence of a Reye-like syndrome (sudden loss of consciousness in children following certain infections) was also described.

Changes in laboratory parameters of liver function (increase in GOT, GPT, LAP, gammaGT, alkaline phosphatase, bilirubin) are seen frequently during therapy, but usually normalize when dosage is adjusted. If clinical symptoms of liver damage (recurrent gastric complaints, vomiting, loss of appetite, fatigue, weakness, jaundice, ascites, hepatic encephalopathy) occur, treatment has to be discontinued immediately.

Very rarely, severe impairment of liver function, including liver failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children, particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks, and usually involved combined therapy with several anticonvulsants.

Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting). Medical evaluation (including measurement of serum amylase) should be undertaken in patients presenting with symptoms suggestive of pancreatitis, and sodium valproate should be discontinued if pancreatitis is
diagnosed. Patients with prior history of pancreatitis should have close clinical supervision. Oedema and - rarely - dysmenorrhoea (menstrual irregularities) and galactorrhoea (abnormal milk discharge from the female breast) may occur.

**OVERDOSE**
Acute overdosage may lead to coma accompanied by areflexia and central respiratory depression. Gastric lavage, administration of activated charcoal, and hemoperfusion are recommended as treatment for overdose. A respirator should be used only under intensive care conditions. The successful use of naloxone as an antidote has been reported.

**PHARMACODYNAMIC PROPERTIES**
Valproic acid (pharmacotherapeutic group NU3A GUI) is a saturated, single-branch fatty acid thus differing in structure from all other annular epileptic drugs. The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA. The activation of glutamic acid decarboxylase and the inhibition of GABA transaminase result in a strong increase in GABA concentrations in the synaptosomes and in the intersynaptic cleft. As an inhibitory neurotransmitter, GABA impedes pre- and postsynaptic discharges and thus prevents convulsive activity from spreading. The psychotropic action of valproic acid results in better visuomotor coordination and enhanced concentration. The efficacy and rapid action of valproic acid in the treatment of acute manic episodes in patients with manic-depressive (bipolar) disorder has been demonstrated in a number of placebo-controlled clinical studies. The efficacy of valproic acid in the long-term treatment of mania (more than 3 weeks) has not yet been studied in controlled clinical trials. The effectiveness of valproic acid in the prophylaxis of migraine has been established in several placebo-controlled double blind studies. Long-term use in this indication has been evaluated over a period of up to 3 years.

**PHARMACOKINETIC PROPERTIES**
Due to their enteric coating, the capsules release the active substance only in the small intestine, where it is absorbed. Peak plasma levels are reached 2-3 hours after administration. Concomitant food-intake does not influence the quantity of absorbed substance. Steady state plasma levels are reached after 2-4 days, depending on the dosage intervals. The therapeutic level is between 50 and 100 mg/l (approx. 300-600 µmol/l) in patients with epilepsy, and between 65 and 125 mg/l (300-750 µmol/l) in patients with affective psychoses or migraine.

About 80-95 % of valproic acid is bound to plasma proteins. Concentrations of valproic acid in cerebrospinal fluid correlate well with the free valproic acid concentration in plasma. Only 1-3 % of the administered dose are excreted in unchanged form via the kidneys. The major part is subject to glucuronization and oxidation in the liver. The metabolites are excreted via the kidneys. Plasma half-life varies individually between 16 hours and is increased in patients with hepatic impairment.
PRECLINICAL SAFETY DATA
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Physicians' Information Leaflet.

SHELF-LIFE 4 years.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25’ C. Do not refrigerate or freeze. Light-protection required — keep in the outer carton.

PRESCRIPTION/DISTRIBUTION DETAILS
Subject to prescription, distribution by pharmacies only.

Use of Convulex:
-Convulex treatment must not be started or terminated without medical advice. Sudden discontinuation of valproic acid may lead to an increase in seizure frequency.
-The dose is determined by your doctor; it is strictly individual. Please take your medicine regularly, do not change or abruptly stop the administration without first consulting your doctor.
-Please consult your doctor immediately, if you are pregnant or plan a pregnancy. Your doctor will decide whether to continue the treatment with Convulex, and whether or not you may breast-feed your baby.
-If you forget to take Convulex once, do not take the double dosage the next time. Go on as usual.
-If you take too high a dose, consult your doctor.
-Do not take the medicine after the expiry date given on the carton.

Interactions
-In order to avoid possible interactions with other medicaments, please inform your doctor or pharmacist if you are taking or have recently taken any other medicines.

Undesirable effects:
-Like all medicines, Convulex may provoke certain undesirable effects. Please report to your doctor or pharmacist any undesirable effect which is not mentioned in this Physicians’ Information Leaflet.

-Do not store above 25’ C. Do not freeze. Keep in the outer carton in order to protect from light and humidity.
-Keep out of the reach and sight of children.