PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

Convulex® Syrup

Convulex® 150 Capsules

Convulex® 300 Capsules

Convulex® 500 Capsules

COMPOSITION

Convulex® Syrup: One ml contains 50 mg sodium valproate
Preservatives: methylhydroxybenzoate 0,1% m/v
propylhydroxybenzoate 0,04% m/v

Convulex® 150: valproic acid (per capsule) 150mg

Convulex® 300: valproic acid (per capsule) 300mg

Convulex® 500: valproic acid (per capsule) 500mg

All the above are sugar-free

PHARMACOLOGICAL CLASSIFICATION

A2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION

The anticonvulsant action of both valproic acid and sodium valproate may be related to increased levels of gamma-aminobutyric acid (GABA) in the brain by inhibiting aminobutyrate aminotransferase. GABA inhibits pre- and post-synaptic discharges.

INDICATIONS

Epilepsy

Convulex® is indicated for generalised seizures as well as for partial (focal) seizures, including complex partial seizures evolving to generalised seizures.

Acute mania in Bipolar I affective disorders.

Treatment of acute manic episodes associated with bipolar disorders in patients intolerant to lithium or with an unsatisfactory response to lithium therapy.

Migraine

Prophylaxis of migraine headaches if other drugs have not shown the desired effect.

CONTRA-INDICATIONS

Known hypersensitivity to valproic acid or sodium valproate.
Hepatic and pancreatic dysfunction.

Use of Convulex® during pregnancy: See SPECIAL PRECAUTIONS - **Women of childbearing age**.

Special caution is required in the following cases:

- Bone marrow abnormalities
- Children younger than 3 years (as they are especially predisposed for hepatic damage) - see **SIDE EFFECTS AND SPECIAL PRECAUTIONS**
- Congenital enzyme defects
- Haemorrhagic diathesis
- Mentally retarded children
- Organic cerebral lesions
- Renal dysfunction
- Severe epileptic seizure types

WARNINGS
(See also **SPECIAL PRECAUTIONS**)

Convulex® may cause hepatic dysfunction including fatal hepatic failure. This may be independent of dosage level and usually occurs during the first 6 months of treatment and children are at greater risk. This may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness

and lethargy. If clinical symptoms of hepatic damage (recurrent epigastric complaints, anorexia, vomiting, fatigue, asthenia, icterus, ascites, hepatic encephalopathy) occur, treatment must be discontinued under the supervision of a physician. Hepatic function impairment may progress in spite of discontinuation of medication.

Sudden discontinuation of valproic acid may lead to an increase in seizure frequency.

INTERACTIONS

Valproic acid displaces **phenytoin, phenobarbitone** and **diazepam** from plasma protein binding, which leads to an increase in free levels of these substances. The metabolism of **diazepam** is inhibited by valproic acid. Serum levels of **primidone** are increased. The effect of **ethosuximide** is potentiated. **Phenytoin, phenobarbitone** and **primidone** lead to increased clearance and reduced plasma levels of valproic acid.

In rare cases concomitant administration of **clonazepam** may induce absence status.

In cases of combination therapy with other **anticonvulsants**, careful determination of blood levels is essential. Concomitant use of **felbamate** leads to increased plasma levels of valproic acid. Concomitant administration of **lamotrigine** increases the elimination half-life of that substance.

Caution must be exercised when administering **naloxone**, since this drug could theoretically also reverse the anti-epileptic effects of **Convulex®** (also see **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**).

Caution is recommended when administering **Convulex®** with other medicines liable to interfere with **blood coagulation**, such as **aspirin**, **heparin** and **warfarin**.

Salicylates replace valproic acid from its serum albumin binding sites and affect its metabolism, which may result in toxic concentrations of valproic acid, that are clinically relevant, especially in children. Concomitant administration of **hepatotoxic drugs** may potentiate the possible adverse effects of valproic acid in the liver

Convulex® does not induce liver enzymes and there have been no reports of loss of efficacy of **oral**

contraceptive agents.

Convulex® may potentiate the effect of **monoamine oxidase inhibitors** (MAOI) and therefore the dosage of such medicine must be lowered when used together with valproic acid.

Both sodium valproate and valproic acid may enhance the effects of **central nervous system depressants** (including **alcohol**), and may reduce the patient's ability to drive vehicles or operate machinery.

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 also to their more rapid metabolism, so that thyroid function tests may incorrectly lead to a suspicion of hypothyroidism.

PREGNANCY AND LACTATION

See **SPECIAL PRECAUTIONS - Women of childbearing age**.

DOSAGE AND DIRECTIONS FOR USE

The dosage (starting with a low initial dose) is determined by the physician, and should not be arbitrarily altered or exceeded. The total daily dose should be administered in divided doses. **Convulex**® capsules should be taken whole, with some liquid, during or after meals.

Epilepsy

Adults:

The initial dose is 600 mg per day in divided doses, increasing by 150 mg per day to a maintenance dose of 1 000 - 1 600 mg per day (approx. 3-5 capsules of 300 mg each or 2 - 3 capsules of 500 mg each).

If adequate control is not achieved after 2 weeks, further increases to a maximum of 2 600 mg per day may be necessary.

Children:

Children weighing less than 20 kg may be given 15 - 20 mg per kg per day. In severe cases, the dosage can be increased at one-week intervals by 5 – 10 mg per kg daily to 40 mg per kg per day, but in these cases the plasma valproate concentration of the patient must be monitored. Should the daily dose exceed 100 mg (e.g. 2 ml of **Convulex® Syrup**), it should be administered in divided doses.

Children weighing more than 20 kg may be given 450 mg daily in divided doses (e.g. 3 x 1 capsule of **Convulex® 150**), gradually increasing to establish control, usually at a level of 20 – 30 mg per kg per day.

Dosage in patients being treated with other anticonvulsant drugs, should be gradually reduced concurrently with the increase of the **Convulex®** dose.

Acute mania in Bipolar I affective disorders.

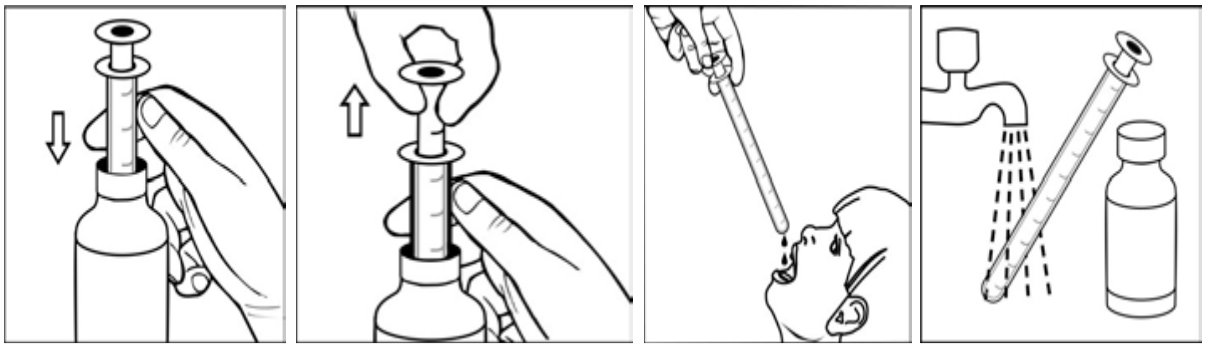
The recommended initial dose is 600 – 900 mg daily, divided into several doses. Highly agitated patients may be treated with up to 1 500 mg per day. Gradual dose increases should then be effected at intervals of 2 to 4 days and accompanied by monitoring of plasma levels.

Migraine (Adults only)

Starting at 300 mg per day in divided doses, the daily dose is slowly increased until the desired therapeutic effect is achieved or side-effects occur. Most patients can be effectively treated with

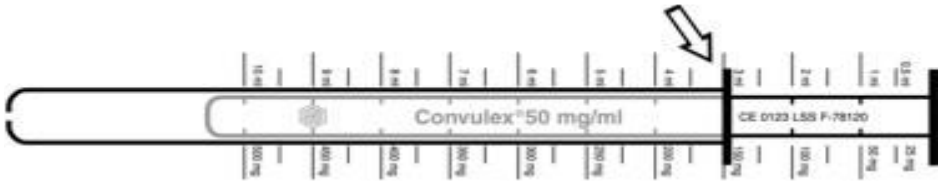
600 – 900 mg per day and this should be accompanied by monitoring of plasma levels.

Directions to use syringe for Convulex® Syrup



1. Push the plunger down completely into the syringe, then insert syringe into the bottle.	2. Pull the plunger up until the mark corresponding to the prescribed dose is reached (graduation in ml and mg). Repeat if necessary.	3. Administer the measured dose directly into the child's mouth or with the help of a spoon or glass. Make sure the complete dose is given.	4. After each use, close the bottle and carefully rinse the syringe with water. Store both syringe and bottle in the carton.

Dosage marks on the syringe



SIDE-EFFECTS AND SPECIAL PRECAUTIONS

SIDE-EFFECTS

Very common (10%); common (1% - <10%); uncommon (0.1% - <1%); rare (0.01% - <0.1%);

very rare (<0.01%), including isolated reports.

Side-effects occur in rare cases and are most frequently seen when plasma levels exceed 100 mg/l or when **Convulex®** is used in combination therapy.

Blood and lymphatic system

Hematological changes reported with valproic acid include thrombocytopenia, inhibition of platelet aggregation, reversible prolongation of bleeding time, red cell hypoplasia, leucopenia, neutropenia, lymphocytosis, hypofibrinogenemia and in very rare cases anaemia and bone marrow depression. Hyperammonaemia, increase in serum glycine levels and decrease in carnitine levels have been reported. Less frequently oedema.

Patients should be monitored for platelet functions before and during **Convulex**® therapy and before elective surgery. Caution is required in surgical or dental interventions, because of a possible increase in bleeding tendency. **Convulex**® should be withdrawn if patients develop spontaneous bruising or bleeding.

Endocrine system

Less frequent reports of dysmenorrhea, galactorrhea, gynaecomastia.

Gastro-intestinal disorders

The most commonly reported side-effects relate to the gastro-intestinal system. Nausea, vomiting and anorexia may occur at the beginning of therapy, but usually disappear with dose adaptation and administration together with, or after meals. Increased appetite and weight gain, gastralgia, gastrospasms, diarrhoea and constipation have also been reported.

Very rare cases of acute pancreatitis have also been reported

Nervous system

Rare side effects include headache, dysarthria, sedation, vertigo, hearing loss, nystagmus, diplopia, involuntary movements, ataxia, asterixis, tonic spasms, tremor, impaired co-ordination.

Rare hyperactivity and aggression.

In isolated cases, states of confusion, stupor and coma were observed a few days after therapeutic plasma levels were reached. In these cases, a paradoxical effect in patients with previous psychic disorders was suspected.

Psychiatric disorders

Less frequent reports of a depressive state.

Skin and subcutaneous tissue

Allergic skin reactions occur very rarely. Individual cases of petechial bleeding, tendency to develop hematoma, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme and transient alopecia with regrowth of curly hair, have been reported. The occurrence of a Reye-like syndrome has also been described.

SPECIAL PRECAUTIONS

Patients experiencing abdominal pain, symptoms of organic damage or hemorrhagic disorders, should have serum amylase and lipase checked. At the first indication of pancreatitis, treatment must be stopped under the supervision of the physician.

Liver function tests, coagulation parameters and determination of serum amylase and lipase, should be carried out before starting therapy, and also at 2-monthly intervals during the first 6 months of therapy. Thereafter, the aforementioned tests should be carried out when the dose is increased. Convulex® should be discontinued if one of the following occurs: hypofibrinogenemia, coagulation disorders, increase in transaminases to their triple value, increases in alkaline phosphatase or serum bilirubin, symptoms or signs of toxic hepatitis. If only transaminases are slightly increased, the dose should be reduced and liver function, as well as coagulation parameters should be monitored.

Renal function and serum ammonia levels should be monitored at regular intervals.

Valproic acid should be used with caution if systemic lupus erythematosus is suspected.

<u>Women of childbearing age</u>

Convulex® has been associated with teratogenicity when given to women in the first trimester of pregnancy. Its use should be avoided in pregnant women and women likely to become pregnant, unless its continued use is considered essential by the prescribing physician. Women who have been exposed to Convulex® in the first trimester of pregnancy should be informed of the risk, and offered prenatal counseling.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Acute overdose may lead to coma, accompanied by areflexia and central respiratory depression. Treatment should include induced vomiting, administration of activated charcoal, gastric lavage, assisted ventilation, forced diuresis and other supportive measures.

Naloxone has been reported to reverse the CNS-depressant effects of overdosage (also see under **INTERACTIONS**).

IDENTIFICATION

Convulex® Syrup: Sugar-free, clear, colourless to slightly yellow syrup, with a peach / raspberry odour and taste

Convulex® 150: Old-rose coloured, enteric-coated, oval, soft gelatine capsule with black imprint “150”

Content of capsule: clear, colourless to slightly yellow liquid.

Convulex® 300: Old-rose coloured, enteric-coated, oval, soft gelatine capsule with black imprint “300”

Content of capsule: clear, colourless to slightly yellow liquid.

Convulex® 500: Old-rose coloured, enteric-coated, oval, soft gelatine capsule with black imprint “500”

Content of capsule: clear, colourless to slightly yellow liquid.

PRESENTATION

Convulex® Syrup: 100ml amber glass bottles

Convulex® 150: Blister packs containing 100 capsules

Convulex® 300: Blister packs containing 100 capsules

Convulex® 500: Blister packs containing 100 capsules

STORAGE INSTRUCTIONS

Store below 25 ℃, protected from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

Convulex® Syrup W/2.5/390

Convulex® 150 Capsules R/2.5/218

Convulex® 300 Capsules R/2.5/219

Convulex® 500 Capsules W/2.5/20

HOLDER OF THE REGISTRATION CERTIFICATE

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