PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

Convulex® Syrup

Convulex® 150 Capsules

Convulex® 300 Capsules

Convulex® 500 Capsules

2 QUALITATIVE AND QUANTITATIVE 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) 150 mg

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

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

All the above are sugar-free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup and capsules.

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 medicines have not shown the desired effect.

4.2 Posology and method of administration

Posology

The dosage (starting with a low initial dose) is determined by the medical practitioner 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 medicines, 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.

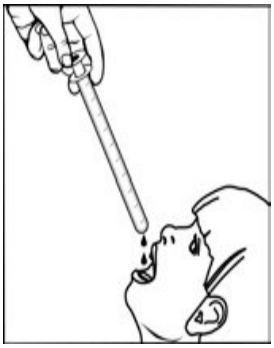
Method of administration

Oral use.

Directions to use syringe for Convulex® Syrup:

1. Push the plunger down completely into the syringe, then insert syringe into the bottle.

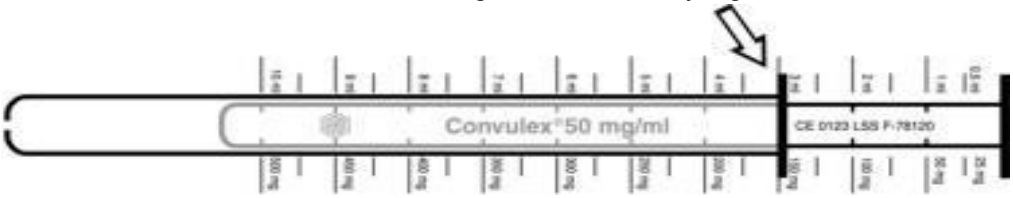
2. Pull the plunger up until the mark corresponding to the prescribed dose is reached (graduation in ml and mg). Repeat if necessary.



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



4.3 Contraindications

- Known hypersensitivity to valproic acid, sodium valproate or to any of the excipients of Convulex® (see section 6.1).
- Active liver disease.

- Personal or family history of severe hepatic dysfunction, especially medicine related.
- Porphyria.
- Pancreatic dysfunction.
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).
- in women of childbearing potential, unless supervised by a medical practitioner experienced in treating these conditions and the patient is informed of the risks of taking Convulex® and the pregnancy prevention program is fulfilled (see section 4.4 and 4.6).
- Women must not use CONVULEX for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.

4.4 Special warnings and precautions for use

Special caution is required in the following cases

- Bone marrow abnormalities

- Children younger than 3 years (as they are especially predisposed for hepatic damage)

- Haemorrhagic diathesis

- Mentally retarded children

- Renal dysfunction

- Organic cerebral lesions

- Severe epileptic seizure types

Pregnancy Prevention Program

Women of childbearing potential

Convulex® has a high teratogenic potential and children exposed *in utero* to Convulex® have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Conditions of the Pregnancy Prevention Program

The medical practitioner must ensure that:

- individual circumstances are evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to Convulex® *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (refer to “Contraception” in this section), without interruption during the entire duration of treatment with Convulex®.
- the patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy, or bipolar disorders.

- the patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timeous discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her medical practitioner in case of pregnancy
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with Convulex® use.

These conditions also concern women who are not currently sexually active unless the medical practitioner considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pharmacists or healthcare professionals must ensure that:

- patients are advised not to stop their Convulex® medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Female children:

- The medical practitioner must ensure that parents/caregivers of female children understand the need to contact the medical practitioner once the female child using Convulex® experiences menarche (see section 4.3).
- The medical practitioner must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for infants exposed to Convulex® *in utero* (see section 4.3).
- In patients who experienced menarche, the medical practitioner must reassess the need for Convulex® therapy annually and consider alternative treatment

options. If Convulex® is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention program must be discussed. Every effort should be made by the medical practitioner to switch female children on Convulex® to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test:

Pregnancy must be excluded before start of treatment with Convulex®. Treatment with Convulex® must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception:

Women of childbearing potential who are prescribed Convulex® must use effective contraception without interruption during the entire duration of treatment with Convulex®. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user-independent form such as an intra-uterine device or implant) or two complementary forms of contraception, which includes a barrier method, should be used.

Individual circumstances should be evaluated in each case, when choosing the contraception method, and involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea, she must follow all the advice on effective contraception.

Annual treatment reviews by a medical practitioner:

The medical practitioner should at least annually review whether Convulex® is the

most suitable treatment for the patient. The medical practitioner should discuss the annual risk acknowledgement form, at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning:

For the indication of epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess Convulex® therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6).

If switching is not possible, the woman should receive further counselling regarding the Convulex® risks for the unborn child, to support her informed decision-making regarding family planning.

In case of pregnancy:

If a woman using Convulex® becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with Convulex® and consider alternative options. Patients with an Convulex®-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Educational materials:

In order to assist healthcare professionals and patients in avoiding exposure to Convulex® during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of Convulex® in women of childbearing potential and includes the details of the pregnancy prevention program.

An annual risk acknowledgement form needs to be completed at time of treatment

initiation and during each annual review of Convulex® treatment by the medical practitioner.

Special warnings

Liver dysfunction

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 medical practitioner. Hepatic function impairment may progress in spite of discontinuation of medication. Sudden discontinuation of Convulex® may lead to an increase in seizure frequency.

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

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.

Pancreatitis

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Convulex® should be discontinued.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines, such as Convulex® in several indications. A meta-analysis of randomised placebo- controlled trials of anti-epileptic medicines has also shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for Convulex®. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Precautions

Haematological

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8).

Renal insufficiency

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Systemic lupus erythematosus

Although immune disorders have only rarely been noted during the use of Convulex®, the potential benefit of Convulex® should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8).

Hyperammonaemia

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Convulex®.

Weight gain

Convulex® very frequently causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8).

Carbapenem medicines

The concomitant use of valproic acid/sodium valproate, as in Convulex®, and carbapenem medicines is not recommended (see section 4.5).

Diabetic patients

Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme

polymerase γ(POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Effects of Convulex® on other medicines

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

Convulex® may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised, and dosage should be adjusted when appropriate.

Phenobarbitone

Convulex® increases phenobarbitone plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbitone doses if sedation occurs and determination of phenobarbitone plasma levels when appropriate.

Primidone

Convulex® increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin

Convulex® decreases phenytoin total plasma concentration. Moreover Convulex® increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore, clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

Carbamazepine

Clinical toxicity has been reported when valproate was administered with carbamazepine as Convulex® may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

Convulex® may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Convulex® might increase the risk of rash.

Zidovudine

Convulex® may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Vitamin K-dependent anticoagulants

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid, as in Convulex®. The prothrombin time should be closely monitored.

Temozolomide

Co-administration of temozolomide and Convulex® may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other medicines on Convulex®

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbitone, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of felbamate and Convulex® may increase valproic acid plasma concentration. Convulex® dosage should be monitored.

Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Convulex® may need adjustment.

In case of concomitant use of Convulex® and highly protein bound medicines (e.g. aspirin), free valproic acid plasma levels may be increased.

The plasma levels of valproic acid, as in Convulex®, may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

Decreases in blood levels of valproic acid, as in Convulex®, have been reported when it is co-administered with carbapenem medicines resulting in a 60 - 100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem medicines in patients stabilised on valproic acid, as in Convulex®, is not considered to be manageable and therefore should be avoided (see section 4.4).

Cholestyramine may decrease the absorption of valproate.

Other interactions

Caution is advised when using Convulex® in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Valproate, as in Convulex®, usually has no enzyme-inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative medicines in women receiving hormonal contraception, including the oral contraceptive pill.

Effects of Convulex® on laboratory parameters

Valproic acid, as in Convulex®, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Convulex® is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Convulex® is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled (see sections 4.3 and 4.4).

Convulex® should not be used in female children, in female adolescents, in women of child-bearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of child-bearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Teratogenicity and developmental effects

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10,73 % of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95 % CI: 8,16 – 13,29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3 %. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most frequent types of malformations include neural tube defects, facial dysmorphia, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalities involving various body systems.

Developmental disorders

Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in pre-school children exposed *in utero* to valproate show that up to 30 – 40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children, female adolescents and woman of childbearing potential (see above and section 4.4).

If a woman plans a pregnancy

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high

peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a medical practitioner experienced in the management of epilepsy.

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.

- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

- Withdrawal syndrome (such as in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate

during the last trimester of their pregnancy.

Breastfeeding

Valproate, as in Convulex®, is excreted in human milk with a concentration ranging from 1 % to 10 % of total maternal serum levels.

Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Convulex® therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. No adverse effects in the nursing infant have been reported. The decision to allow the patient to breastfeed should be taken with regard to all the known facts.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate, as in Convulex®, (see section 4.8). Valproate, as in Convulex®, administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Convulex® may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5).

4.8 Undesirable effects

a. Summary of the safety profile

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.

b. Tabulated summary of adverse reactions

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Thrombocytopenia
	Less frequent	Anaemia, leucopenia, pancytopenia, reduction of fibrinogen, reversible increase in bleeding time, spontaneous bruising or bleeding
Immune system disorders	Less frequent	Allergic reactions (ranging from rash to hypersensitivity reactions)
Metabolism and nutrition disorders	Frequent	Hyperammonaemia (see section 4.4)
	Less frequent	Obesity
Nervous system disorders	Less frequent	Sedation, lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions, diplopia, encephalopathy and coma, reversible extrapyramidal

System organ class	Frequency	Adverse reactions
		symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy, dose-related ataxia and fine postural tremor, increase in alertness, aggression, hyperactivity and behavioural deterioration
Ear and labyrinth disorders	Less frequent	Hearing loss
Vascular disorders	Less frequent	Vasculitis
Gastrointestinal disorders	Frequent	Nausea, gastralgia, diarrhoea
	Less frequent	Pancreatitis, sometimes lethal (see section 4.4)
Hepato-biliary disorders	Frequent	Increased liver enzymes
	Less frequent	Liver dysfunction, severe liver damage, including hepatic failure sometimes resulting in death (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent	Nail and nail bed disorders
	Less frequent	Cutaneous reactions such as exanthematous rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema

System organ class	Frequency	Adverse reactions
		multiforme, transient hair loss, hirsutism, acne
Musculoskeletal and connective tissue disorders	Less frequent	Decreased bone mineral density, osteopenia, osteoporosis and fractures
Renal and urinary disorders	Less frequent	A reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria)
Reproductive system and breast disorders	Less frequent	Amenorrhoea and irregular periods, gynaecomastia
Congenital, familial and genetic disorders	Less frequent	Congenital malformations and developmental disorders (see section 4.4 and section 4.6)
General disorders	Less frequent	Non-severe peripheral oedema, increase in weight (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8 & at drugsafety_ZA@acino.swiss

4.9 Overdose

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 section 4.5).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: anti-epileptics, fatty acid derivates, ATC code: N03A G01.

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.

5.2 Pharmacokinetic properties

Absorption

The half-life of valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children.

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 - 100 mg/litre (278 - 694 micromol/litre). This reported range may depend on time of

sampling and presence of co-medication.

Distribution

The percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Convulex® may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already stated in other sections of the professional information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule:

Gelatine

Glycerol monostearate

Hydrochloric acid

Hydrogenated hydrolysed starch

Macrogol 6000

Methacrylic acid-ethylacrylate copolymer

Red iron oxide (E 172)

Titanium dioxide (E 171)

Triethyl citrate

Syrup:

Lycasin

Saccharin sodium

Sodium cyclamate

Sodium chloride

Sodium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Convulex 150 capsules: 36 months

Convulex 300 capsules: 60 months.

Convulex 500: 36 months.

Syrup: 36 months.

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture.

6.5 Nature and contents of container

Convulex® Syrup: 100 ml amber glass bottles

Convulex® 150: Blister packs containing 100 capsules

Convulex® 300: Blister packs containing 100 capsules

Convulex® 500: Blister packs containing 100 capsules

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

1686

8 REGISTRATION NUMBERS

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

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 February 2004

10 DATE OF REVISION OF THE TEXT

26 January 2023