PROFESSIONAL INFORMATION

CONVULEX® has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the foetus resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities. Exposure to CONVULEX® in *utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention-deficit hyperactivity disorder (ADHD).

CONVULEX® treatment must be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and must not be prescribed if the relevant risk minimisation measures/Pregnancy Prevention Programme cannot be implemented and supervised and patients are not committed to adhere to these measures.

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, oval soft capsule without grey imprinting "150.

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

Convulex® 300: Old rose, oval soft capsule with grey imprinting "300".

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

Convulex® 500: Old rose, oblong soft capsule without grey imprinting "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.

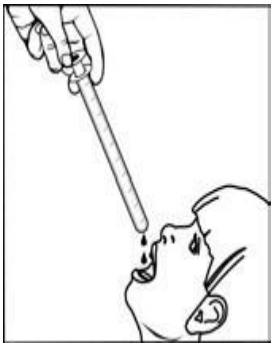
Directions to use syringe for Convulex® Syrup:



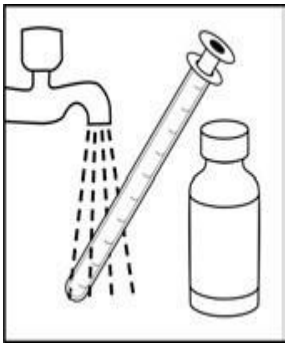
1. Push the plunger down completely into the syringe, then insert syringe into the bottle.



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

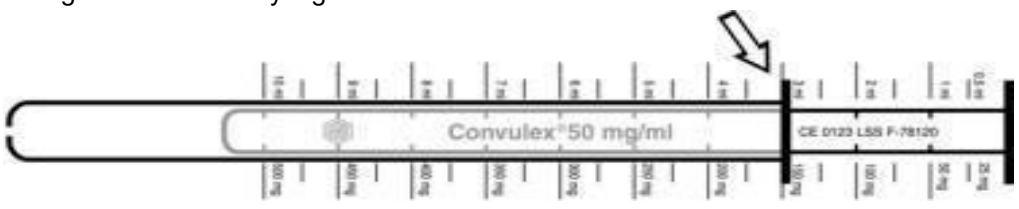


3. Administer the measured dose directly into the child's mouth or with the help of a spoon or glass.
Make sure the complete dose is given.



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.
- Hepatic 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.
- Patients with known urea cycle disorders (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4 Patients at risk of hypocarnitinemia).

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 received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with Convulex® use. (Annual Risk Acknowledgement Form)

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 health care professionals must ensure that:

- The patient card is provided with every Convulex® dispensing and that the patients understand its content.
- 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 health care 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.

Estrogen-containing products:

Convulex® does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased Convulex® efficacy. Medical practitioners should monitor clinical response (seize control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of valproate serum level (see section 4.5).

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.

Male children and men

All male patients and/or carers should be made aware of the potential risk to children born to men treated with valproate in the 3 months before conception (see also section 4.6), of the

risk of infertility in men (see sections 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, doctors and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation. Female partners to male patients should be tested for pregnancy. Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their doctors or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for health care professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

Special warnings

Severe liver damage

Conditions of occurrence

Cases of severe liver damage, which may result in fatalities, have been reported. Experience

in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic disorders including mitochondrial disorders, such as carnitine deficiency, urea cycle disorders, POLG mutations or degenerative disease.

After the age of 3 years, the incidence of occurrence is reduced and decreases with age. In most cases, such liver damage occurred during the first 6 months of treatment, the period of maximum risk being 2-12 weeks.

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity (see also section 4.5). Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing valproate, but the potential benefit of valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see sections 4.4 and 4.5).

Suggestive signs

Clinical symptoms are essential for early diagnosis. In particular, the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above *Conditions of occurrence*).

- Non-specific symptoms, usually of sudden onset such as asthenia, anorexia, lethargy, and/or drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- In patients with epilepsy, recurrence of seizures.

Patients (or their family in the case of children) should be instructed to report any such signs immediately to a medical practitioner should they occur. Investigations, including clinical examination and laboratory assessment of liver function, should be undertaken immediately.

Detection

Liver function tests should be carried out before starting therapy and periodically monitored

during the first 6 months of therapy (see also section 4.5).

Increased liver enzymes may be noted, particularly at the beginning of therapy. More extensive biological investigations (including prothrombin index/prothrombin time [INR/PT]) are recommended in patients developing increased liver enzymes. An adjustment of dosage (decrease) may be needed when appropriate and tests should be repeated as necessary. Amongst usual investigations, tests which reflect protein synthesis, particularly INR/PT, are most relevant. Confirmation of an abnormally low INR/PT, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires discontinuation of Convulex® therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued, since they follow the same metabolic pathway.

Patients with known or suspected mitochondrial disease:

Convulex® 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, acute liver failure and liver-related deaths have been associated with Convulex®. treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for 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, ophthalmoplegia, 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).

Urea cycle disorders and risk of hyperammonaemia

Convulex® may cause 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®. (see sections 4.3 and 4.4: *Patients at risk of hypocarnitinemia* and *Severe liver damage*)
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity.

Patients at risk of hypocarnitinemia:

Convulex® administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonaemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia, when treated with Convulex®. include patients with metabolic disorders, including mitochondrial disorders related to carnitine (see warnings on *Patients with known or suspected mitochondrial disease* and *Urea cycle disorders and risk of hyperammonaemia*), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to immediately report any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed.
Patients with systemic primary carnitine deficiency and corrected for hypocarnitinemia should be treated with Convulex® only if the benefits of Convulex® treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinemia should be implemented.
Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Convulex® Carnitine supplementation should be considered in these patients (see sections 4.5, 4,8 and 4.9)

Pancreatitis

Pancreatitis, which may be severe and result in fatalities, has been 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 immediately should signs of suicidal ideation or behaviour emerge.

Carbapenem medicines

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

Aggravated convulsions:

Some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus) or the onset of new types of convulsions with Convulex® In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

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

New development and exacerbation of systemic lupus erythematosus (SLE) may occur. The potential benefit of Convulex® should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8).

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).

Severe Cutaneous Adverse Reactions and Angioedema

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed, and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

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.

Alcohol use during treatment with Convulex®

Alcohol intake is not recommended during treatment with Convulex®.

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.

Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

Clozapine

Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

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.

Felbamate

Convulex® may decrease the felbamate mean clearance by up to 16 %.

Rufinamide

Convulex® may lead to an increase in plasma levels of rufinamide.

This increase is dependent on concentration of valproic acid. Caution should be exercised, particularly in children, as this effect is larger in this population.

Propofol

Convulex® may lead to an increased blood level of propofol. When co-administered with Convulex®, a reduction of the dose of propofol should be considered.

Nimodipine

Concomitant treatment of nimodipine with Convulex® may increase nimodipine plasma concentration by 50 %.

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-depressants and neuroleptics

Anti-depressants and neuroleptics may antagonise the anti-epileptic activity of Convulex® by lowering the seizure threshold. This may require Convulex® dosage adjustments.

Anti-epileptics

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 decrease valproic acid clearance by 22-50 % and consequently increase the valproic acid plasma concentration. Convulex® dosage should be monitored. Valproic acid metabolite levels may be increased in case of concomitant use with **phenytoin** or **phenobarbital** (phenobarbitone). Therefore, patients treated with any of these two medicines together with Convulex® should be carefully monitored for signs and symptoms of hyperammonaemia.

Mefloquine

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.

Highly protein-bound medicines

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

Vitamin K-dependent factor anticoagulants

Close monitoring of INR (prothrombin index) should be performed in case of concomitant use of vitamin K-dependent factor anticoagulants (e.g. warfarin) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by Convulex®.

Cimetidine or erythromycin

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.

Carbapenem antibiotics (imipenem/meropenem/ertapenem)

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, sometimes associated with convulsions. 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 4.3). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood level should be performed.

Rifampicin

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, Convulex® dosage adjustment may be necessary when it is co-administered with rifampicin.

Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma levels when co-administered with Convulex®.

Although formal interaction studies have not been performed, available data suggest a reduction ranging from 40 % to 77,5 % in valproate plasma levels.

Patients using protease inhibitors such as ritonavir for the treatment of HIV infection should be carefully monitored for decreased control of their epilepsy/mood status of bipolar patients if also treated with Convulex®.

Cholestyramine

Cholestyramine may decrease the absorption of valproate.

Estrogen-containing medicines

Estrogen-containing medicines, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased Convulex® efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when adding or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels (see section 4.4).

Metimazole

Metamizole may decrease valproate serum levels when co-administered with Convulex® which may result in potentially decreased valproate clinical efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Methotrexate

Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Other interactions

Risk of liver damage

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4).

Concomitant use of Convulex® and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).

In patients of all ages receiving cannabidiol at doses 10 to 25 mg/kg and valproate concomitantly, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19 % of patients.

Appropriate liver monitoring should be exercised when Convulex® is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

Topiramate and acetazolamide

Concomitant administration of Convulex® and topiramate or acetazolamide has been associated with encephalopathy, metabolic acidosis and/or hyperammonaemia. Patients treated with these two medicines should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.

Pivalate-conjugated medicines

Concomitant administration of Convulex® and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see section 4.4: *Patients at risk of hypocarnitinemia*). Concomitant administration of these medicines with Convulex® is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

Quetiapine

Co-administration of Convulex® and quetiapine my increase the risk of neutropenia/ leucopenia.

Estrogen- and/or progestogen-containing medicines

CONVULEX® usually has no enzyme-inducing effect. As a consequence, Convulex® does not reduce efficacy of estrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

Newer anti-epileptics (including topiramate and acetazolamide)

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

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

Treatment of epilepsy

- Convulex® is contraindicated during pregnancy, unless there is no suitable alternative treatment.
- Convulex® is contraindicated in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Treatment of bipolar disorder

- Convulex® is contraindicated during pregnancy.
- Convulex® is contraindicated in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4)

Women of childbearing potential / contraception in males and females

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

Pregnancy exposure risk related to valproate

In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.

Valproate was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

Congenital malformations from in utero exposure

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 of major congenital malformations in children after in utero exposure to anti-epileptic polytherapy, including Convulex® is higher than that of anti-epileptic medicines polytherapy not including Convulex®. This risk is dose-dependent in Convulex® monotherapy, and available data suggest it is dose-dependent in Convulex® polytherapy. However, 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.

In utero exposure to Convulex® may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

In utero exposure to Convulex® may result in eye malformations (including colobomas, microphthalmos). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neurodevelopmental disorders

Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. This risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when Convulex® is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When Convulex® is administered in polytherapy with other anti-epileptic

medicines during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.

The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When Convulex® is administered in monotherapy, 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 from a population-based study 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 to the unexposed population in the study.

Available data from another population-based study show that children exposed to valproate in utero are at an increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1,5-fold) compared to the unexposed population in the study.

Female children, female adolescents and woman of childbearing potential aged under 55 years (see above and section 4.4).

If a woman plans a pregnancy

For the epilepsy indication, 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.

For the bipolar disorder indication, if a woman is planning to become pregnant a medical practitioner experienced in the management of bipolar disorder must be consulted.

Treatment with Convulex® should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered (see section 4.3).

Pregnant women

Convulex® as treatment for bipolar disorder is contraindicated for use during pregnancy.

Convulex® 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/pre-natal medicine 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.
- If appropriate, folate supplementation should be started before pregnancy and at relevant

dosage (5 mg daily) as it 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 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; ~~A~~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, menstrual disorders, polycystic ovaries and increased testosterone levels and impairment of ovarian function and of fertility 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). Fertility dysfunctions may not always be reversible after treatment discontinuation. Very low concentrations of valproate have been detected in semen of males on treatment with Convulex®.

It is not known with certainty if fertility would be affected by Convulex® treatment in children less than 18 years of age, as valproate may interact with sex hormones.

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. Where applicable, the following frequency rating has been used: Very common (≥ 1/10); common (≥ 1/100; < 1/10); uncommon (≥ 1/1000; < 1/100); rare (≥ 1/10 000; < 1/100); very rare (< 1/10 000).

b. Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Not know

Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)		myelodysplastic syndrome	
Blood and lymphatic system disorders	anaemia, thrombocytopenia	pancytopenia**, leucopenia, ** bone marrow dysfunction (including pure red cell aplasia, agranulocytosis, macrocytic anaemia, macrocytosis reduction of fibrinogen, reversible increase in bleeding time, spontaneous bruising or bleeding	
Endocrine disorders		syndrome of inappropriate secretion of ADH (antidiuretic hormone) (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or increased androgen) hypothyroidism	
Metabolism and nutrition disorders	hyponatraemia, increased weight (see section 4.4)	hyperammonaemia, obesity	Hypocarnitinaemia (see section 4.3 and 4.4)
Psychiatric disorders	confusional state, hallucinations, aggression, agitation*, disturbance in attention*	abnormal behaviour*, psychomotor hyperactivity*, learning disorder*	
Nervous system disorders	tremor, extrapyramidal disorder, stupor*, somnolence, convulsions*, memory impairment, headache, nystagmus, dizziness	coma, ataxia, encephalopathy, lethargy, reversible parkinsonism, paraesthesia, and aggravated convulsions (see section 4.4) reversible dementia associated with reversible cerebral atrophy, cognitive disorder	

Eye disorders		diplopia	
Ear and labyrinth disorders	deafness		
Vascular disorders	haemorrhage (see section 4.4 and 4.6)	vasculitis	
Respiratory, thoracic and mediastinal disorders		pleural effusion	
Gastrointestinal disorders	nausea, vomiting, gingival disorder (especially gingival hyperplasia), stomatitis, upper abdominal pain, gastralgia, diarrhoea**	pancreatitis, sometimes lethal (see section 4.4)	
Hepato-biliary disorders	liver injury (see section 4.4)		
Skin and subcutaneous	hypersensitivity, alopecia, nail and nail bed disorders	angioedema, rash-hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth) toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme**,** drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	
Musculoskeletal and connective tissue disorders		decreased bone mineral density**, osteopenia**, osteoporosis and fractures** development and worsening of systemic lupus erythematosus, rhabdomyolysis	
Renal and urinary disorders	urinary incontinence	renal failure, enuresis, tubulointerstitial nephritis, 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	dysmenorrhoea	amenorrhoea, irregular periods, gynaecomastia, male infertility, polycystic ovaries, impairment of ovarian function and of fertility in females	
Congenital, familial and genetic disorders		congenital malformations and developmental disorders (see **section 4.4 and section 4.6)**	
General disorders and administration site conditions		hypothermia, peripheral oedema	
Investigations		coagulation factors decreased (at least one), abnormal coagulation tests**	acquired Pelger-Huet anomaly*

* Acquired Pelger-Huet anomaly has been reported in cases with and without myelodysplastic syndrome.

****c. Description of selected adverse reactions***

Hepato-biliary disorders

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also sections 4.2, 4.3 and 4.4). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4).

Gastrointestinal disorders

(Nausea, gastralgia, diarrhoea) frequently occur at the start of treatment. These problems can usually be overcome by taking Convulex® capsules with or after food.

Blood and lymphatic system disorders

The blood picture returned to normal when the drug was discontinued.

Isolated reduction of fibrinogen or reversible increase in bleeding time have been reported, usually without associated clinical signs and particularly with high doses (valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also

section 4.6).

Metabolism and nutrition disorders

Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Convulex® should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).

Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Nervous system disorders

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Ear and labyrinth disorders

Hearing loss, either reversible or irreversible has been reported; however, a cause-and-effect relationship has not been established.

Musculoskeletal and connective tissue disorders

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on longterm therapy with medicinal products containing valproate. The

mechanism by which valproate affects bone metabolism has not been identified.

Renal and urinary disorders

There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to metabolic acidosis, glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Reproductive system and breast disorders

Very rarely gynaecomastia has occurred.

Congenital, familial and genetic disorders

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Investigations

Coagulation factors decreased, abnormal coagulation tests (e.g. prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

d. Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients**.**

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 Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. You can also report side effects to Acino Pharma via email on drugsafety_ZA@arceralifesciences.com.

4.9. Overdose

Signs of acute massive overdose may include coma, with muscular hypotonia, hyporeflexia, miosis and respiratory depression, metabolic acidosis, hypotension and circulatory collapse/shock (also see section 4.8).

Deaths have occurred following massive overdose.

Seizures have been reported in the presence of very high plasma levels of valproate. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Convulex® formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic and supportive:

Administration of activated charcoal may be useful following ingestion. Cardiorespiratory monitoring assisted ventilation and other supportive measures are recommended.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully.

In cases of Convulex® overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.

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.

In cases where measurement of plasma levels is considered necessary, trough plasma levels should be used for therapeutic monitoring.

Valproic acid concentration in cerebrospinal fluid is close to free plasma concentration.

Placental transfer (see section 4.6)

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta, to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the foetuses, was similar to or slightly higher than that in the mothers.

Metabolism:

When given in therapeutic doses, most of the medicine is converted to the conjugate ester of glucuronic acid, while mitochondrial metabolism, principally by means of beta-oxidation, accounts for the remainder. Some of the metabolites have anticonvulsant activity.

Sodium valproate is mainly excreted in urine following metabolism via glucuro-conjugation and beta-oxidation.

Sodium valproate does not increase its own degradation, neither that of other medicines such as estrogen- and progestogen- containing medicines.

Elimination:

The elimination half-life of sodium valproate varies from approximately 8 to 20 hours. It is usually shorter in children. In patients with severe renal insufficiency, it may be necessary to alter the dosage in accordance with free plasma valproic acid levels.

Paediatric population:

Based on published literature, in paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults. In children aged 2 – 10 years, valproate clearance is 50 % higher than in adults. Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults.

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.

Genotoxicity:

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay) and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown.

Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to

valproate.

However, this data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus untreated epileptic patients, provided contradictory results.

The biological significance of an increase in SCE frequency is not known.

Carcinogenicity:

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 mg/kg/day and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

Reproductive and developmental toxicity:

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats and rabbits.

In published literature, behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure to clinically relevant doses/exposures of valproate. In mice, behavioural changes have also been observed in the second and third generations, albeit less pronounced in the third generation, following an acute *in utero* exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility:

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 1 250 mg/kg/day and 150 mg/kg/day, respectively.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the

maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to paediatric population is unknown.

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: 36 months.

Convulex® 500: 36 months.

Convulex® 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

24 July 2026