ORFIRIL® INJECTION

Qualitative and quantitative composition

3 ml solution (1 ampoule) contains 300mg sodium valproate List of excipients: disodium edetate, water for injection

Pharmaceutical form

Solution for injection

Clinical particulars Therapeutic indications Treatment of:

- Generalized seizures in the form of absences, myoclonic and tonic-clonic seizures,
- Partial and secondary generalized seizures.

Combination treatment of other forms of seizures.

Orfiril® injection solution is used if oral sodium valproate therapy cannot be given.

Note:

In infants, sodium valproate is the first-line drug only in exceptional cases; it should be used only with great caution and after careful consideration of the risk-benefit ration and, if possible, as monotherapy.

Posology and method of administration

Orfiril® injection is intended exclusively for intravenous administration.

The dosage should be determined according to age and weight and monitored individually by the physician on the basis of concentration determinations. Close monitoring of plasma levels and - if necessary - dosage adjustments have to be performed during the change-over to a parenteral therapy, during the parenteral therapy and during the switch back to oral therapy, in particular in such patients receiving higher doses of valproate or in patients receiving medicinal products potentially influencing the metabolism of valproate. Therapeutic efficacy is usually reached at plasma levels between 50 and 100 mg/L (340-700 µmol/L). The mean daily dosages during maintenance treatment are as follows:

Children	30 mg sodium valproate/kg body weight
Adolescents	25 mg sodium valproate/kg body weight
Adults	20 mg sodium valproate/kg body weight

Higher maintenance doses for children and adolescents arise from higher valproate clearence values in these patients.

Starting of treatment and continuation of maintenance treatment in patients on valproate:

Children and adults

To a new patient, initially a 5-10 mg/kg bolus dose as a slow intravenous (i.v.) injection over 3-5 minutes of sodium valproate is recommended. The dosage should be elevated by 5 mg/kg every 4 - 7 days to the recommended maintenance dose for each age group, or until a satisfactory clinical response is achieved. The total daily dose should be divided in three to four single administrations. To a patient previously on the medicinal product, an equivalent of the usual oral single dose (mg) as a slow intravenous (i.v.) injection over 3-5 minutes or as a short infusion is recommended; if necessary, the administration is continued as repeated injections

every 6 hours, or as a slow intravenous infusion at 0.6-1 mg/kg/h until the patient can take the medicine orally. For children, a maintenance dose of 30 mg/kg/day of sodium valproate is recommended, but if adequate seizure control is not achieved, the dose can be elevated to 40 mg/kg/day. In such cases, plasma valproic acid levels should be monitored frequently. It should be noted that in infants younger than 2 months, the elimination half-life of valproic acid might be up to 60 h. This should be taken in consideration when increasing the dosage to maintenance treatment. The maximal dose recommended for adults is 2400 mg/day.

In patients with renal failure, the rise in free valproic acid in the plasma must be taken into consideration and the dose reduced accordingly.

Method of administration

Orfiril® injection may be given by slow intravenous injection or by infusion in 0.9 % saline or 5% dextrose.

Duration of treatment

The intravenous administration of **Orfiril®** injection should be replaced by oral therapy as soon as practicable. In the clinical studies, there is no experience of more than a few days treatment with **Orfiril®** injection.

Contraindications

Sodium valproate must not be used in patients with:

- Hypersensitivity to sodium valproate or to any of the excipients (see section 6.1)
- Previous or present liver disease and/or severe current dysfunction of the liver or pancreas
- Liver disease in family history
- A history of a sibling having died from liver dysfunction during sodium valproate treatment - Porphyria
- In patients with blood coagulation disorders or thrombocytopenia

Special warnings and precautions for use

Sodium valproate must be used only with special care (relative contraindication):

- In infants and children in whom concomitant treatment with several antiepileptics is necessary
- In patients with bone marrow damage
- In children and adolescents with multiple handicaps and severe forms of epilepsy
- In patients with metabolic diseases, particularly with hereditary enzyme deficiency diseases
- In patients with systemic lupus erythematodes
- In patients with insufficient renal function and hypoproteinaemia

In rare cases, severe liver or pancreatic damage with a fatal outcome has been observed in children and adolescents particularly in combination therapy with other antiepileptics. Those most frequently affected are infants and children below the age of 3 years suffering from severe epileptic seizures, particularly in the presence of brain damage, mental retardation and/or a hereditary metabolic disease. Sodium valproate should be administered with special care and

as monotherapy in this patient group. Experience has shown that above this age (particularly after the age of 10 years) the frequency of liver diseases declines substantially. In the majority of cases, liver damage was observed within the first 6 months of treatment, particularly between weeks 2 and 12, and mostly associated with concomitant use of other antiepileptics.

Severe or fatal liver damage may be preceded by non-specific symptoms such as an increase in the frequency of seizures, physical malaise, loss of appetite, averseness for usual food or valproate, epigastric pain, nausea, vomiting, localised or generalised oedema of various types, haematoma/epistaxis, fatigue, jaundice and lethargy. The occurrence of these symptoms should be closely monitored.

Sodium valproate treatment must be discontinued immediately if severe liver dysfunction or pancreatic damage is suspected. Tripling of the serum aspartate aminotranferase (AST) and alanine aminotransferase (ALT) values, moderate (1.5-2-fold) increase of ALT or AST accompanied by an acute infection with fever, abnormally prolonged prothrombin time (particularly in the presence of other changes in laboratory parameters, such as fibrinogen and clotting factors (mainly factor VIII) or elevated bilirubin or liver enzymes), elevation of alkaline phosphatase and bilirubin values and changes in protein values can be considered to be criteria for discontinuation.

In infants, sodium valproate is the first-line active substance only in exceptional cases; it should be used only with great caution and after careful consideration of the risk-benefit ratio and, if possible, as monotherapy.

The following time schedule for clinical and laboratory examinations applies for children:
Before the onset of treatment, then once monthly for 6 months, and after this twice at 3-month intervals. In addition, it is recommended that the parents/guardians have telephone contact to the attending physician regularly between the laboratory controls to ensure early detection of toxic or other clinical symptoms.

Laboratory tests to be performed before commencing treatment: Complete blood count (CBC) incl. platelets, coagulation values (thromboplastin time = P-TT-SPA, fibrinogen INR, factor VIII and associated factors), serum lipase, serum amylase, AST, ALT, alkaline phosphatase, total bilirubin, protein, blood glucose.

Laboratory tests during treatment:
In case of no clinical anomalies, determination of CBC (including platelets) and liver aminotransferases is sufficient. However, every second examination should include a test evaluating coagulation parameters (see above).

After 12 months of treatment without anomalies, 2 to 3 examinations (clinical and laboratory, respectively) in a year generally are sufficient.

In adolescents and adults, the risk of severe or even fatal complications is very small. Therefore, once a thorough clinical examination and laboratory tests have been made before the onset of

treatment (as in children), it is recommended that CBC (including platelets), liver and pancreatic function tests be made at regular intervals, in particular during the first six months.

However, the attending physician should not rely exclusively on the blood chemistry parameters since they are not necessarily abnormal in all cases. The clinical history and examination are crucially important for evaluation. It must also be borne in mind that liver enzyme values may be elevated transiently in some individuals with no evidence of liver dysfunction, particularly at the start of treatment.

The treatment with sodium valproate may lead to increased plasma ammonia concentrations (hyperammonaemia). If hyperammonaemia is associated with symptoms such as apathy, somnolence, vomiting, hypotension and increase in seizure frequency, ammonium and valproic acid plasma levels should be determined and, if necessary, the drug should be withdrawn. If the presence of an enzymatic disorder of the urea cycle is suspected, plasma ammonium levels should be measured before initiation of therapy with valproate.

The use of sodium valproate only rarely leads to reactions of the immune system. Nevertheless, in patients who show signs of lupus erythematosus, it should only be administered after careful consideration of the risks and benefits.

Occasionally, especially with high doses, prolonged bleeding and/or thrombocytopenia may occur. Therefore, patients with unexpected bleeding of the mucous membranes or increased tendency towards haematoma should undergo further examinations.

Determination of platelets, thromboplastin time, bleeding time and fibrinogen is recommended before surgical or dental procedures.

Patients with pre-existing bone marrow damage must be closely monitored.

In patients with renal failure, as well as in patients with hypoproteinaemia, the rise in free valproic acid in the plasma must be taken into consideration and the dose reduced accordingly. Careful injection techniques are mandatory to prevent accidental intraarterial, paravenous, subcutaneous or intramuscular injections, which result in tissue necrosis.

If non-dose-dependent side effects occur, the medicine should be discontinued.

Nausea, sometimes accompanied by vomiting and loss of appetite, may occur rarely at the onset of treatment. These side effects are transient on their own or after dose reduction.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do no exclude the possibility of an increased risk for sodium valproate. 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.

Note:
It has been shown that sodium valproate stimulates the replication of human immunodeficiency virus in some in vitro studies. The clinical significance of this is not understood

Interaction with other medicinal products and other forms of interaction

If sodium valproate is combined with other antiepileptics, it should be noted that reciprocal effects on plasma concentrations are possible: enzyme-inducing antiepileptics such as phenobarbitone, phenytoin and carbamazepine increase valproic acid excretion and therefore reduce its effect. Concomitant use with inducing medicinal products can increase the risk of liver toxicity and hyperammonaemia.

Felbamate increases dose-dependently the plasma concentration of free valproic acid linearly about 18 %.

Mefloquine increases the breakdown of valproic acid and also has potentially spasmogenic effects. Concomitant administration can therefore lead to epileptic seizures.

The serum concentration of valproic acid can be elevated by the concomitant administration of cimetidine, fluoxetine and erythromycin. However, cases of decreased valproic acid serum levels with coadministration of fluoxetine have been reported as well.

Antimicrobial drugs belonging to the carbapenem group can decrease the serum concentration of sodium valproate.

Concomitant use of sodium valproate and anticoagulants (warfarin) or acetylsalicylic acid may increase the tendency to bleeding. Acetylsalicylic acid also reduces the plasma-protein binding of valproic acid. Regular monitoring of blood coagulation is therefore recommended. Sodium valproate and acetylsalicylic acid should not be administered concomitantly in fever and pain, particularly in babies and infants.

It is possible that potentially hepatotoxic medicinal products, including alcohol, may exacerbate liver toxicity.

In combination therapy with lithium, the concentrations of both active substances in plasma should be monitored regularly.
The valproate-induced rise in phenobarbitone concentration, which may manifest as severe sedation, is of special clinical importance. If this occurs, the dose of phenobarbitone or primidone must be reduced (primidone is partly metabolised to phenobarbitone). Therefore, careful clinical monitoring is recommended throughout the first 24 hours of treatment of status epilepticus and during the first 15 days of combination therapy in electic antiepileptic treatment. Valproic acid may cause a transient considerable increase of free (unbound) phenytoin levels but as a result of concomitant use, total phenytoin levels decrease. This has, however, usually no clinical significance since the amount of free phenytoin remains sufficient. Valproic acid can increase carbamazepine-10,11-epoxide levels to a toxic region despite carbamazepine level within the therapeutic range. In concomitant use, nimodipine level may increase significantly because of metabolic inhibition.

Valproic acid inhibits the metabolism of lamotrigine. Therefore, the dosage of lamotrigine must be reduced in concomitant use.
The risk of skin reactions appears to be increased if drugs containing valproic acid are combined with lamotrigine.

Sodium valproate increases the concentration of ethosuximide in plasma, with risk for undesirable effects. When the two medicinal products are combined, control of plasma levels of ethosuximide is recommended.

Valproic acid may increase the plasma concentration of zidovudine, with the increased risk of toxic reactions.

Valproic acid may increase the plasma concentration of felbamate by approximately 50 %. The metabolism and protein binding of other active substances such as codeine is also affected.
When combined with barbiturates, benzodiazepines (e.g. diazepam, lorazepam, clonazepam) neuroleptics or antidepressants, sodium valproate may potentiate the central-suppressant effect of these medicinal products.

As sodium valproate is partly metabolised to ketone bodies, the possibility of false-positive results for tests of ketone-body excretion should be borne in mind in diabetics with suspected ketoacidosis.

In women taking hormonal contraceptives, no tendency for plasma concentrations of oral contraceptives to decrease has been identified, since sodium valproate does not have any enzyme-inducing effects.

In children, serum levels of phenytoin may increase following concurrent administration of clonazepam and valproate.

Absences occurred in patients with a history of absence seizures who were treated concomitantly with medicinal products containing valproate and clonazepam.

In healthy volunteers, valproate displaces diazepam from plasma albumin binding sites and inhibits its metabolism. In combination therapy, the concentration of unbound diazepam may increase and a 25% decrease in clearance from plasma and 20% decrease in distribution volume of the unbound fraction of diazepam may occur. However, the half-life remains unchanged.

In healthy volunteers, concurrent treatment with valproate and lorazepam produces a reduction in plasma clearance of lorazepam by up to 40%.

Catatonia occured in a patient with schizoaffective disorder under triple treatment with valproate, sertraline and risperidone.

Pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic drugs in general.

The risk of birth defect is increased by factor 2 - 3 in the offspring of mothers treated with an antiepileptic. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk linked to valproate

Congenital abnormalities including neural tube defects (spina bifida, meningomyelocele) and other midline defects like hypospadias in male children, skeletal deformities (facial dysmorphia - also in conjugation with mental retardation, limb malformations) and cardiac deformities have been reported in offspring born to mothers with epilepsy who have been treated with valproate. Bilateral aplasia of the radius would appear to be a rare but specific effect of pharmaceuticals containing valproate. A foetal antiepileptic syndrome has been described. Some data have suggested an association between in-utero valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

In the case of women of a childbearing age, attention should be drawn to the necessity of planning and monitoring a pregnancy even before the start of treatment.

Prenatal diagnostic measures for the early detection of damage (ultrasound and alpha-fetoprotein determination) are recommended.

A combination with other antiepileptics increases the risk of deformities. Therefore valproic acid should be administered in the form of a monotherapy whenever this is possible.

Folic acid supplementation, prior to pregnancy may reduce the incidence of neural tube defects in infants born to women at high risk. Women should consider taking 5 mg folic acid /day when she plans to become pregnant.

Orfiril® treatment should not be interrupted during pregnancy without the agreement of the doctor, as a sudden discontinuation of the therapy or uncontrolled reduction in the dose may lead to epileptic seizures in expecting mothers which may prove harmful to her and/or the unborn child.

Abnormal pregnancy outcomes tend to be associated with higher total daily dosage and size of an individual dose. There is evidence that high plasma peak levels and the size of an individual

dose are associated with neural tube defects. The incidence of neural tube defects rises with increasing dosage, particularly above 1000 mg/day.

Valproic acid passes through the placenta and reaches higher concentrations in the foetal plasma than in the maternal plasma. If **Orfiril®** is indispensable, it should be administered in the lowest seizure-controlling dose during pregnancy, particularly in the first trimester. As deformities are very probably caused by peak concentrations in the plasma, the daily dose should be distributed over several small doses throughout the day if the patient intends to bear the child, particularly between the 20th and 40th day of pregnancy. In addition, there should also be regular monitoring of the plasma concentration, as the plasma concentrations may evidently be subject to considerable fluctuations during the course of the pregnancy even if the dosage remains.

Withdrawal symptoms in neonates whose mothers were treated with valproic acid have been reported.

There are reported cases of disturbances to blood coagulation (haemorrhagic syndrome) in neonates whose mothers were treated with valproate during pregnancy. This syndrome is attributed to hypofibrinogenaemia. There have also been reports of fatalities due to the total absence of fibrin. The hypofibrinogenaemia may occur together with a reduction in coagulation factors. However, this syndrome must be distinguished from a drop in vitamin K-dependent coagulation factors caused by enzyme inducers such as phenobarbitone. For this reason the blood platelets, fibrinogen level and coagulation factors in the newborn should be examined and coagulation tests carried out.

Lactation:
Valproic acid passes into the mother's milk. However, the quantities are small and are not generally associated with any risk to the child, so that weaning is not necessary as a rule."

Effects on ability to drive and use machines

During treatment with sodium valproate, reaction time may be impaired. This should be taken in account when increased attention is required, for example during driving and operating machinery.

Undesirable effects

The undesireable effects that can result from use of **Orfiril®** injection include all of those associated with oral forms of valproate.
With parenteral administration also burning sensation at the injection site might occur.
The most commonly reported undesirable effects for sodium valproate are gastrointestinal disturbances, occuring in approximately 20% of the patients. Cases of severe (and even fatal) liver damage have been observed particularly in children treated with high doses or in combination with other antiepileptics.

The undesireable effects have been classified in order of frequency by the mentioned convention: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Blood and the lymphatic system disorders

Common:	Thrombocytopenia, leucopenia.
Uncommon:	Haemorrhage
Very rare:	Bone marrow disorders, reduced concentration of fibrinogen and/or coagulation factor VIII, impaired platelet aggregation, prolonged bleeding time, lymphocytopenia, neutropenia,
	pancytopenia, anaemia.

Immune system disorders

Rare: Lupus erythematodes and vasculitis

Allergic reactions have been reported (see also skin and subcutaneous tissue disorders).

Endocrine disorders

Rare: Hyperandrogenism.

Metabolism and nutrition disorders

Common:	Hyperammonemia, increased or decreased weight, increased or reduced appetite.
Rare:	Hyperinsulinaemia, low levels of insulin-like growth-factor-
	binding protein I, oedema, hypothermy.
Very rare:	Abnormal findings in thyroid function tests have been reported.
	Their clinical relevance is unclear.

Psychiatric disorders

Rare: Irritability, hallucinations, confusion.

Nervous system disorders

Common:	Drowsiness, tremor, paraesthesias, sleepiness.
Uncommon:	Transient coma, in some cases associated with increased seizure frequency.
Rare:	Headache, hyperactivity, spasticity, ataxia, stupor,
	hypersalivation.

Very rare: Encephalopathy*[1], dementia associated with cerebral atrophy, parkinsonian syndrome (reversible), decreased hearing, tinnitus.

Gastrointestinal disorders Very common: Pain, nausea, vomiting.

Rare: Diarrhoea, pancreatitis.

Hepato-biliary disorders

Common: Changes in liver tests.

Rare: Severe liver damage*[2].

Skin and subcutaneous tissue disorders

Common:	Transient hair loss, hair fading and curling of the hair.
Rare:	Exanthema, erythema multiforme.
Very rare:	Stevens-Johnson syndrome, Lyell's syndrome.

Renal and urinary disorders

Very rare: Fanconi's syndrome, enuresis in children.

Reproductive system and breast disorders

Common: Amenorrhoea.

Rare: Ovarian polycystic disease.

General disorders and administration site conditions

Rare: Inflammation with or without pain at the injection site

After erroneous intra-arterial, intramuscular, subcutaneous or perivenous injection tissue disorders may occur.

Dizziness may occur when administered intravenously. With parenteral administration also burning sensation at the injection site might occur. Uncommonly, taste disturbances, and rarely, unspecified pain and singultus may occur. There have been isolated reports of metabolic acidosis.

*[1]In rare cases encephalopathy of unknown pathogenesis that developed shortly after use of a medicinal product containing valproic acid and was reversible after withdrawal of the medicinal product has been observed. In a few such cases, increased levels of ammonia and, in the case of combination with phenobarbital, an increase in phenobarbital levels have been described. In isolated cases, particularly with high doses or in combination with other antiepileptics (particularly with phenytoin) chronic encephalopathies have been found. These were associated with neurological symptoms and disorders of high cortical functions, whose aetiology could also not be adequately explained.

*[2]Particular attention must be paid to the following signs of liver damage: a reduction in anti-epileptic effect characterised by the recurrence of or increase in epileptic seizures, feeling of physical weakness, loss of appetite, nausea or repeated vomiting, epigastric pain of unknown origin, generalised or localised oedema formation, listlessness, disturbances of consciousness with confusion, agitation and disturbances of movement. In very rare cases, pancreatic damage with similar clinical features has also been observed. Children and infants should be carefully monitored for these clinical features. If the symptoms mentioned above are persistent or severe, appropriate laboratory investigations should be carried out in addition to a thorough clinical examination (see Special warnings and precautions for use).

Overdose

Whenever intoxication is evaluated, the possibility of multiple intoxication as a result of the possible ingestion of several medicinal products, for example in suicide attempts, should be considered.

At a reference range (340-700 µmol/l), valproic acid has relatively low toxicity. Individual, rare cases of acute and chronic over-dosage with a fatal outcome have been reported in the literature.

Symptoms of overdose
The symptoms of intoxication are characterised by confusion, sedation or even coma, myasthenia and hypo- or areflexia. Hypotension, myosis, cardiovascular and respiratory disorders, cerebral oedema, metabolic acidosis, hypocalcaemia and hypernatraemia have also been observed in individual cases. In adults and children, high plasma levels provoke abnormal neurological reactions and behavioural changes.

Management of overdose
No specific antidote is known. Treatment must therefore be limited to general measures to remove the active substance from the body and to support vital functions. In case of oral intoxication, vomiting should be induced or a gastric lavage administered and activated charcoal given if possible within 30 minutes after ingestion. In this case, intensive medical supervision is necessary. Haemodialysis or forced diuresis may be useful. Peritoneal dialysis has little effect.

There is insufficient experience on the efficacy of haematogenic charcoal perfusion or complete plasma replacement and blood transfusion. For this reason, particularly in children, intensive in-patient treatment is recommended, with no special detoxification techniques but with monitoring of the plasma concentration.

PhaRmaCOLOgICaL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic agents; Fatty acid derivatives; Valproic acid
ATC-code: N03A G01
Valproic acid is an antiepileptic which bears no structural resemblance to the active constituents of other anticonvulsants. Valproic acid has demonstrated anticonvulsant efficacy in laboratory animals and humans. An increase in GABAmediated inhibition by a presynaptic effect on GABA metabolism and/or a direct postsynaptic effect on the ion channels of the neuronal membranes is the accepted explanation.

Multidrug-transporter-proteines remove drugs from the brain and may decrease the concentration of antiepileptic drugs at the place of action. Expression of to many of these multidrug-transporters may result in resistance to the drug and therefore in the development of status epilepticus or epilepsy resistant to treatment. It was demonstrated in preclinical and in-vitro studies, that valproate is not removed from the brain by multidrug-transporters. Therfore development of a resistance to treatment by multidrug-transporters is unlikely for valproate.

Valproic acid is slightly soluble in water (1:800), sodium valproate is readily soluble in water (1:0.4).

Pharmacokinetic properties

Plasma levels, plasma protein binding, distribution

With intravenous administration maximum plasma levels are reached almost immediately.

The relationship between dose and plasma concentration is linear. There is no direct correlation between plasma valproic acid levels and efficacy but the reference range is usually considered to be of the order of 340-700 µmol/l. Above 700 µmol/l, increased undesirable effects may be expected. Steady-state plasma levels are reached within 3-4 days if the treatment starts with a maintenance dose.

The volume of distribution is age-dependent and is generally 0.13 - 0.23 l/kg, and 0.13 - 0.19 l/kg in adolescents.

Up to 90 - 95 % of valproic acid is plasma-protein-bound, mainly to albumin. Protein binding decreases at higher dosages. Plasma protein binding is lower in elderly patients and in patients with kidney or liver dysfunction. In one study, raised values of free active constituent (8.5 to more than 20 %) were observed in patients with significantly reduced renal function.

During pregnancy, hepatic and renal clearances rise with an increase in the volume of distribution in the third trimester, with a possible fall in the plasma concentration despite the same dosage. In addition, a change in the plasma protein binding has been observed during the course of pregnancy with an increase of the free (therapeutically active) valproic acid.

Valproic acid crosses the placenta and passes into breast milk. In the steady state, the concentration in breast milk is approximately 10 % of the plasma concentration.

The valproic acid concentration in cerebrospinal fluid is 10 % of the prevailing plasma concentration.

Metabolism, elimination

Biotransformation takes place by glucuronidation and by beta-, omega-, and omega1-oxidation. Approximately 20 % of the administered dose is excreted in the urine as the glucuronide ester. There are more than 20 metabolites, those resulting from omega oxidation being regarded as hepatotoxic. Less than 5 % of an administered valproic acid dose appears unchanged in the urine. The main metabolite is 3-ketovalproic acid, up to 3 - 60 % of which appears in the urine.

Plasma clearance, elimination half-life

In healthy subjects plasma clearance is 5 - 10 ml/min; clearance increases if enzyme-inducing antiepileptics are ingested (in patients with epilepsy, a level of 12.7 ml/min was measured). When used as monotherapy, the active substance has an average plasma half-life of 12 - 16 hours, which does not change during long-term treatment.

Neonates and infants up to the age of 18 months have plasma half-lives of between 10 and 67 hours. The longest half-lives were observed immediately after birth; over the age of 2 months, the values approach those of adults.

The half-life is prolonged in patients with liver disease. In the case of over-dosage, half-lives of up to 30 hours have been observed.

Preclinical safety data

Chronic toxicity
Testicular atrophy, degeneration of the vas deferens and insufficient spermatogenesis as well as lung and prostate gland changes have been observed in chronic toxicity studies in rats and dog. The clinical relevance of these findings is unknown.

Valproic acid has been found to be teratogenic in mice, rats and rabbits. Studies of the mutagenic potential have shown no mutagenic effect. In carcinogenic studies in rats and mice, increased incidences of subcutaneous fibrosarcoma were observed at high doses in male rats.

PhaRmaCEUTICaL PaRTICULaRS

Incompatibilities
Orfiril injection should not be administered via the same intravenous line with other medicinal products .

Shelf life
Three years

Special precautions for storage
Unopened ampules should be stored below 25°C.

Chemical and physical in-use stability has been demonstrated for 3 days at 2022°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated antiseptic conditions. Do not freeze.

Special precautions for disposal and handling
Orfiril® injection is ready to use. It may be injected slowly in to the vein (i.v.) or infused after dilution with 0.9% sodium chloride or 5% dextrose solution intravenously.
Dilutions must be made using aseptic techniques.
Orfiril® injection is for single use only . Unused solution should be discarded. Prior to use the diluted solution should be visually inspected. Only clear solutions without particles should be used.

Nature and contents of container
5 one-point-cut (OPC) colourless glass ampoules containing 3 ml solution for injection