SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
ORFIRIL INJECTION

2. Qualitative and quantitative composition
VALPROIC ACID (AS SODIUM) 100 mg/ml

One ampoule with 3 ml solution for injection contains 300 mg of sodium valproate (equivalent to 260.28 mg of valproic acid).

One ampoule with 10 ml solution for injection contains 1,000 mg of sodium valproate (equivalent to 867.6 mg of valproic acid).

Excipient(s) with known effect:

1 ampoule with 3 ml solution for injection contains 1.81 mmol (41.6 mg) sodium.

1 ampoule with 10 ml solution for injection contains 6.0 mmol (138.8 mg) sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Solution for injection / Infusion

4. Clinical particulars
4.1. 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.

4.2. Posology and method of administration

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.

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**.

4.3. Contraindications
Orfiril injection is contraindicated in the following situations:

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Porphyria
- 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).
- Patients with known urea cycle disorders (see section 4.4)
- in pregnancy unless there is no suitable alternative treatment (see sections 4.4 and 4.6).
- in women of childbearing potential
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

4.4. Special warnings and precautions for use
Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for sodium valproate.

Therefore, patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

The concomitant use of sodium valproate and carbapenem is not recommended (see section 4.5).

Aggravated convulsions:

As with other antiepileptic drugs, 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 valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Hepatic dysfunction

Conditions of occurrence

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsants therapy, are infants and in particular young children under the age of 3 and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4) or degenerative disease associated with mental retardation. After the age of 3, the incidence of occurrence is significantly reduced and progressively decreases with age. The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk liver toxicity (see also section 4.5).

Additionally, salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome).

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

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

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, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures

These are an indication for immediate withdrawal of the drug.

Patients (or their carers) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection

Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem at risk, and those with a prior history of liver disease. Upon changes in concomitant medicinal products (dose increase or additions) that are

known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5). Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decreases in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) require cessation of **Orfiril injection** therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Patients at risk of hypocarnitinaemia

Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic 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 hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 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 report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.
Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative.
In these patients, carnitine monitoring should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Carnitine supplementation should be considered in these patients. See also section 4.5, 4.8 and 4.9.

Pancreatitis

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).

Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, **Orfiril injection** should be discontinued.

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 (see sections 4.2 and 5.2).

Systemic lupus erythematosus

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

Urea cycle disorders Hyperammonaemia

When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of risk of hyperammonaemia with sodium valproate. Weight gain

Sodium valproate very commonly 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 minimize it (see section 4.8).

Diabetic Patients

Sodium valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies: this may give false positive in the urine testing of possible diabetics.

Patients with known or suspected mitochondrial disease

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

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, 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).

Alcohol

Alcohol intake is not recommended during treatment with valproate.

Excipient with known effect

This medicinal product contains 41.6 mg sodium per **3 mL ampoule**, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 138.8 mg sodium per **10 mL ampoule**, equivalent to 7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5. Interaction with other medicinal products and other forms of interaction

Effects of **Orfiril injection** on other drugs

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

Orfiril injection may potentiate the effect of other psychotropics, such as **antipsychotics, monoamine oxidase inhibitors, antidepressants and benzodiazepines**. Therefore, clinical monitoring and the dosage of other psychotropics should be adjusted when appropriate. In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium
Orfiril injection has no effect on serum lithium levels.

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

Phenobarbital
Sodium valproate increases **phenobarbital** plasma concentrations and sedation may occur, particularly in children. Clinical monitoring is recommended throughout the first 15 days of combined treatment with an immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital levels when appropriate.

Primidone
Sodium valproate increases **primidone** plasma levels causing an exacerbation of side effects, e.g. sedation; these signs cease with long term treatment. Clinical monitoring is recommended especially when initiating combined therapy with dosage adjustment as necessary.

Phenytoin
Orfiril injection decreases **phenytoin** total plasma concentration and increases the free form of phenytoin leading to possible overdosage symptoms. Therefore, clinical monitoring is recommended with the free form of phenytoin being measured, when phenytoin plasma levels are determined.

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

Lamotrigine
Orfiril injection reduces the metabolism of **lamotrigine** and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended, and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

Felbamate
Valproic acid may decrease the **felbamate** mean clearance by up to 16%.

Rufinamide
Valproic acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

Propofol
Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

Zidovudine
Orfiril injection may raise **zidovudine** plasma concentration leading to increased zidovudine toxicity.

Nimodipine
In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

Vitamin K-dependent anticoagulants
The anticoagulant effect of **warfarin** and other **coumarin anticoagulants** may be increased following displacement from plasma protein binding sites by valproate. The prothrombin time should be closely monitored.

Temozolomide
Co-administration of **temozolomide** and **Orfiril injection** may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on **Orfiril injection**

Antiepileptics
Antiepileptics with enzyme inducing effects e.g. **phenytoin**, **phenobarbital**, **carbamazepine**, decrease valproate plasma levels. Plasma levels should be monitored, and dosage adjusted accordingly.

Valproic acid metabolite levels may be increased in the case of concomitant use with **phenytoin** or **phenobarbital**. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of **felbamate** and **Orfiril injection** decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. **Orfiril injection** dosage should be monitored.

Anti-malaria agents
Mefloquine and **chloroquine** increases valproate metabolism and therefore epileptic seizures may occur in combined therapy. The dosage of sodium valproate may need adjustment.

Highly protein bound agents
Free valproate levels may be increased in the case of concomitant use with highly protein bound agents e.g. **acetylsalicylic acid**.

Cimetidine or erythromycin
Valproate plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with ***cimetidine*** or ***erythromycin***.

Carbapenem antibiotics (such as imipenem, panipenem and meropenem)
Decreases in blood levels of valproic acid have been reported when it is co-administered with **carbapenem agents** resulting in a 60 %–100 % decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilized on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Colestyramine
Colestyramine may decrease the absorption of valproate.

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

Protease inhibitors
Protease inhibitors such as **lopinavir** and **ritonavir** decrease valproate plasma level when co-administered.

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives
Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in

decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.
On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Metamizole

Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers 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) and consider monitoring valproate serum levels as appropriate.

Other interaction

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 valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4). Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used 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).

Newer anti-epileptics (including topiramate and acetazolamide)
Caution is advised when using **Orfiril injection** in combination with newer **antiepileptics** whose pharmacodynamics may not be well established.

Concomitant administration of valproate and **topiramate** or **acetazolamide** has been associated with encephalopathy and/or hyperammonaemia. Careful monitoring of signs and symptoms is advised in particularly at- risk patients such as those with pre-existing encephalopathy.

Pivalate-conjugated medicines
Concomitant administration of valproate and **pivalate-conjugated medicines** (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

Quetiapine
Co-administration of **Orfiril injection** and **quetiapine** may increase the risk of neutropenia/leucopenia.

4.6. Fertility, pregnancy and lactation

Teratogenicity and Developmental Effects

Pregnancy Exposure Risk related to valproate

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
A meta-analysis (including registries and cohort studies) showed that approximately 11 % of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3%).
The risk of major congenital malformations in children after *in utero* exposure to antiepileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.
This risk is dose dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate 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 common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment or deafness 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 did not recover.

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

Neuro-Developmental disorders

Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopmental disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated women with epilepsy.
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 valproate is administered in monotherapy, studies in 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 antiepileptics. 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 is 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 3-fold) and childhood autism (approximately 5-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 increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

Female children and women of childbearing potential (see above and section 4.4)

Oestrogen-containing products
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

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

Pregnant women
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:
- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

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

<u>Risk in the neonate</u>

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital 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 is excreted in human milk with a concentration ranging from 1 % to 10 % of 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 breast-feeding or to discontinue/abstain from **Orfiril injection** therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).
Valproate administration may also impair fertility in men (see section 4.8).
Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

4.7. Effects on ability to drive and use machines

Use of **Orfiril injection** may provide seizure control such that the patient may be eligible to hold a driving license.
At the start of treatment with sodium valproate, at higher dosages or with a combination of other centrally acting drugs, reaction time may be altered to an extent that affects the ability to drive or to operate machinery, irrespective of the effect on the primary disease being treated. Patients should be warned of the risk of transient drowsiness. This is especially the case when taken during anticonvulsant polytherapy, concomitant use of benzodiazepines or in combination with alcohol.

4.8. Undesirable effects

Frequency categories are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Congenital, familial and genetic disorders

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

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Rare:	myelodysplastic syndrome

Hepato-biliary disorders

Common:	liver injury (see section 4.4); increased liver enzymes, particularly early in treatment, and may be transient (see section 4.4)
Not known:	severe liver damage, including hepatic failure sometimes resulting in fatalities (see sections 4.2, 4.3 and 4.4)

Gastro-intestinal disorders

Very common:	nausea, occurs a few minutes after intravenous injection with spontaneous resolution within a few minutes
Common:	vomiting, gingival disorder, (mainly gingival hyperplasia), stomatitis gastralgia, diarrhoea

	These frequently occur at the start of the treatment, but usually disappearing after a few days without discontinuing treatment.
Uncommon:	pancreatitis, sometimes lethal (see section 4.4)

Psychiatric disorders

Common:	confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare:	abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Nervous system disorders:

Very common:	tremor
Common:	extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, dizziness may occur a few minutes after intravenous injection; it disappears spontaneously within a few minutes.
Uncommon:	coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4)
Rare:	reversible dementia associated with reversible cerebral atrophy, cognitive disorder

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 uncommonly 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 anticonvulsants, 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.

Endocrine disorders

Uncommon:	Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased)
Rare:	hypothyroidism (see section 4.6)

Metabolism and nutrition disorders

Common:	hyponatraemia, weight increased*

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

Rare:	hyperammonaemia* (see section 4.4), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, 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 **Orfiril injection** 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).

Not known:	hypocarnitinaemia (see section 4.3 and 4.4)

Blood and lymphatic system disorders

Common:	anaemia, thrombocytopenia (see section 4.4)
Uncommon:	pancytopenia, leucopenia
Rare:	bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

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

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (**Orfiril injection** 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).).

Skin and subcutaneous tissue disorders

Common:	hypersensitivity, transient and/or dose related alopecia (hair loss). Regrowth normally begins within 6 months, although the hair may become more curly than previously.
	nail and nail bed disorders
Uncommon:	angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)
Rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders

C*ommon*:	dysmenorrhea
Uncommon:	amenorrhea
Rare:	male infertility, polycystic ovaries
Very rare:	gynaecomastia

Vascular disorders

Common:	haemorrhage (see section 4.4. and 4.6)
Uncommon:	Vasculitis

Eye disorders

Rare:	diplopia

Ear and labyrinth disorders

Common:	deafness, a cause and effect relationship has not been established

Renal and urinary disorders

Common:	urinary incontinence
Uncommon:	renal failure
Rare:	enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with **Orfiril injection** therapy, but the mode of action is as yet unclear

General disorders and administration site conditions

Uncommon:	hypothermia, non-severe oedema peripheral

Musculoskeletal and connective tissue disorders

Uncommon:	bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with **Orfiril injection**. The mechanism by which **Orfiril injection** affects bone metabolism has not been identified.

Rare:	systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4)

Respiratory, thoracic and mediastinal disorders

Uncommon:	pleural effusion

Investigations

Rare:	coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9. Overdose

Symptoms

Cases of accidental and deliberate overdosage with oral therapy have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness. Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times the maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However, some deaths have occurred following massive overdose.

Symptoms may however be variable, and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the **Orfiril injection** formulations may lead to hypernatraemia when taken in overdose.

Management

Hospital management of overdose should be symptomatic, including cardio-respiratory-gastric monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion.
In case of valproate overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalize ammonia levels. Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, Haemodialysis and haemoperfusion have been used successfully.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Fatty acid derivatives

ATCcode: N03AG01

The mode of action of valproic acid in epilepsy is not fully understood but may involve an elevation of gamma-amino butyric acid levels in the brain.

In certain in-vitro studies, it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of sodium valproate on HIV replication ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40–100 mg/L (278–694 µmol/L). This reported range may depend on time of sampling and presence of co-medication.

Per definition, with intravenous injection the bioavailability amounts to 100. The half-life is 8–20 h in most patients but can in exceptional cases be considerable lower. It is usually shorter in children.

Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. 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 and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults.

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

Steady-state concentration is normally achieved after treatment in 3 - 5 days. A satisfactory effect is most often achieved at 40 – 100 mg/litre (278 – 694 micromol/litre), but the patient's overall situation must be considered. The reported range may depend on time of sampling and presence of co-medication. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of **Orfiril injection** may not be clearly correlated with the total or free (unbound) plasma valproic acid levels. The CFS concentration is up to 10% of the plasma concentration. The percentage of free (unbound) drug is usually between 6 and 15% of the total plasma levels. Sodium valproate is metabolised to a great extent and is excreted in the urine as conjugated metabolites.

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 fetuses, was similar to or slightly higher than that in the mothers.

Valproic acid passes into breast milk but is not likely to influence the child when therapeutic doses are used.

5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral

administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.

Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproduction toxicology

Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioural abnormalities have been reported in the first generation offspring of mice and rats after in utero exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

In repeat-dose toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration at doses of 1250 mg/kg/day and 150 mg/kg/day, respectively.

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). Based on these data, juvenile animals were not considered more susceptible to testicular findings than adults. Relevance of the testicular findings to paediatric population is unknown.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. However, male infertility has been identified as an undesirable effect in humans (see sections 4.6 and 4.8).

6. Pharmaceutical particulars

6.1 List of excipients

Water for injections
Disodium edetate

6.2 Incompatibilities

Orfiril injection solution for injection should not be administered via the same intravenous line as other IV additives.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution or reconstitution according to the directions: Chemical and physical in-use stability has been demonstrated for 3 days at 20 - 22°C. From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be not longer than 24 hours at 2 to 8°C, unless dilution has taken place in and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25 ^{0}C.

Do not freeze.

6.5 Nature and contents of container

Glass (type I) ampoule containing 3 ml or 10 ml solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For infusion of **Orfiril injection** solution for injection it may be diluted in 0.9% saline or 5% dextrose.

Prior to use **Orfiril injection** solution for injection and the diluted solution should be visually inspected. Only clear solutions without particles should be used.

The contents of the vial are for single use only

7. Manufacturer

Desitin Arzneimittel GmbH

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8. Marketing authorization holder

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9. Marketing authorization number(s)

117-73-29852

10. Revised in June 2024 according to MOHs guidelines.