1. Name of the medicinal product
Orfiril injection

2. Qualitative and quantitative composition
Sodium valproate 100mg/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

4. Clinical particulars

4.1 Therapeutic indications

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.

4.2 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.

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 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, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).

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).

4.4 Special warnings and precautions for use

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 antiepileptic 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 not 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.

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 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 due to the risk liver toxicity.

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

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. 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.

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).

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 minimise 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.

Carnitine palmitoyltransferase (CPT) type II deficiency

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Orfiril injection.

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.

Sodium content

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 stabilised 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.

Other interaction

Orfiril injection usually has no enzyme-inducing effect; as a consequence, Orfiril injection does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral **contraceptive pill**.

Caution is advised when using Orfiril injection in combination with newer **antiepileptics** whose pharmacodynamics may not be well established.

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

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.

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 suggest that antiepileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

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

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most 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.

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

Studies in preschool 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 are limited data on the long term outcomes.

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

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

Female children 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 (see section 4.2).

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.

Risk in the neonate

• Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by 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). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

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 licence.

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, diplopia

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 (see section 4.4). In such cases further investigations should be considered.

Blood and lymphatic system disorders

Common:	anaemia, thrombocytopenia (see section 4.4)
Uncommon:	pancytopenia, leucopenia

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

Rare:	bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

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

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).

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

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. In massive overdose, 10 to 20 times the maximum therapeutic levels, there may be serious CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis. A favourable outcome is usual, however some deaths have occurred following massive overdose.

The symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. 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.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10–12 hours following ingestion. Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

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

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. In infants under 2 months the half-life can be prolonged up to 60 hours. 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

Acute toxicity

Depending on the species of the animal and mode of administration the LD_{50} is between 0.5 – 1.5g/kg body weight. The symptoms observed included, for example, ataxia, sedation, hypothermia, catalepsy, co-ordination disorders and vomiting.

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 at dosages of more than 250 mg/kg in rats and 90 mg/kg in the dog. In rats, at 200 mg/kg p.o., morphological hepatocytes changes were seen. At 750 mg/kg i.p., functional liver disorders and, among other things, hyperammonaemia, occurred.

Carcinogenic and mutagenic potential

Carcinogenic studies have been conducted in the rat and mouse. At very high doses, increased subcutaneous fibrosarcoma was observed in male rats.

Studies of mutagenic potential have shown no mutagenic effect.

Reproduction toxicology

Valproic acid has been found to be teratogenic in mice, rats, hamsters, monkeys and rabbits. The effects occur primarily as skeletal (palatal cleft, costal and vertebral fusion) and renal malformations, in mice also as encephalocele and malformation of the neural tube. Malformations have also been observed in neurulation studies in chicken embryo in vitro.

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

6. Pharmaceutical particulars

6.1 List of excipients

Disodium edetate

Water for injections

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 controlled 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

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

Weg Beim Jager 214,

D22335 Hamburg

Germany

8. Marketing authorization holder

Megapharm Ltd,

P.O.B 519 Hod Hasharon 4510501

Israel

9. Marketing authorization number(s)

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