WHAT IS ORFIRIL LONG

Orfiril long acid affects chemicals in the body that may be involved in causing seizures.

Orfiril long acid is used to treat various types of seizure disorders. Orfiril long acid is sometimes used together with other seizure medications.

Orfiril long acid is also used to treat manic episodes related to bipolar disorder (manic depression), and to prevent migraine headaches.

Orfiril long acid may also be used for purposes not listed in this medication guide.

Mania

Orfiril long (divalproex sodium) is a valproate and is indicated for the treatment of the manic episodes associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility.

The efficacy of Orfiril long was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania.

The safety and effectiveness of Orfiril long for long-term use in mania, i.e., more than 3 weeks, has not been demonstrated in controlled clinical trials. Therefore, healthcare providers who elect to use Orfiril long for extended periods should continually reevaluate the long-term usefulness of the drug for the individual patient.

Epilepsy

Orfiril long is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Orfiril long is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without

other detectable clinical signs. Complex absence is the term used when other signs are also present.

Migraine

Orfiril long is indicated for prophylaxis of migraine headaches. There is no evidence that Orfiril long is useful in the acute treatment of migraine headaches. Important Limitations

Because of the risk to the fetus of decreased IQ, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition.

Orfiril long is contraindicated for prophylaxis of migraine headaches in women who are pregnant.

HOW SHOULD I USE ORFIRIL LONG?

Use Orfiril long as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Orfiril long comes with an extra patient information sheet called a Medication Guide. Read it carefully. Read it again each time you get Orfiril long refilled.
- Take Orfiril long by mouth with or without food. If stomach upset occurs, take with food to reduce stomach irritation.
- Swallow Orfiril long whole. Do not break, crush, or chew before swallowing.
- Orfiril long works best if it is taken at the same time each day.
- Continue to take Orfiril long even if you feel well. Do not miss any doses.
- If you are taking Orfiril long to treat seizures, do not suddenly stop taking it; this may cause an increased risk of severe seizures. If you need to stop Orfiril long or add a new medicine, your doctor will gradually lower your dose.
- If you miss a dose of Orfiril long, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once.

Ask your health care provider any questions you may have about how to use Orfiril long.

ORFIRIL LONG DESCRIPTION

Each Orfiril long enteric coated tablet contains sodium valproate 200 mg.

Each Orfiril long syrup contains sodium valproate 200 mg per 5 mL.

Each Orfiril long 400 mg powder for injection/infusion contains freeze dried powder: Sodium valproate (DCI) 400 mg per vial and solvent: Water for injection 4 mL per ampoule.

Each Orfiril long Chrono 200 mg contains sodium valproate 133.2 mg and Orfiril long acid 58.0 mg per tab.

Each Orfiril long Chrono 300 mg contains sodium valproate 199.8 mg and Orfiril long acid 87.0 mg corresponding to 300 mg of sodium valproate for 1 tablet.

Each Orfiril long Chrono 500 mg contains sodium valproate 333.0 mg and Orfiril long acid 145.0 mg corresponding to 500 of sodium valproate for 1 tablet.
Excipients/Inactive Ingredients: *Orfiril long EC Tablet:* Povidone, talc, calcium silicate, magnesium stearate, hypromellose 6, citric acid anhydrous, macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid, violet lake solids, industrial methylated spirits, purified water.

Orfiril long Chrono CR Tablet: Hypromellose, ethylcellulose, hydrated silica. *Film Coat:* Violet coat (opadry 04-S-6705), containing: Titanium dioxide (E171), erythrosine BS aluminum lake (E127), indigo carmine aluminum lake (E132), iron oxide black (E172), hypromellose (E464), macgrogel 400, purified water*.

*Not detected in final formulation.

Syrup: Sorbitol powder, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, sodium saccharin, sucrose, Flavour IFF cherry 740, Ponceau 4R (E124) and purified water.

Powd for Inj: None.

ORFIRIL LONG DOSAGE

Tablet/Syrup: Usual requirements are as follows: ***Adults:*** Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1,000 mg to 2,000 mg per day, ie 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2,500 mg per day.

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day.

Children under 20 kg: 20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma Orfiril long acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored. Orfiril long syrup should be used in this group of patients.

Mania: Initially dosage should start with 600 mg daily increasing by 200 mg/day at three-day intervals until control is achieved. This is generally within the range 1,000 to 2,000 mg/day (ie 20 to 30 mg/kg/day).

Where adequate control is not achieved within this range the dose may be further increased to 2,500 mg/day.

Powd for Inj: **Epilepsy:** Daily dosage requirements vary according to age and body weight. To reconstitute, inject the solvent provided (4ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.

Each vial of Orfiril long
Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded.

Orfiril long

Intravenous should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion by PVC, polyethylene or glass containers.

Patients already satisfactorily treated with Orfiril long may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2,500 mg/day.

Orfiril long

Intravenous should be replaced by oral Orfiril long therapy as soon as practicable.

Children: Daily requirement for children is usually in the range 20-30 mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40 mg/kg/day but only in patients in whom plasma Orfiril long acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma Orfiril long acid levels.

Patients with Renal Insufficiency: should be adjusted according to concentrations may be misleading.It may be necessary to decrease dosage. Dosage clinical monitoring since monitoring of plasma

Patients with Hepatic Insufficiency: Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included Orfiril long acid.

Salicylates should not be used in children under 16 years. In addition in conjunction with Orfiril long, concomitant use in children under 3 years should be avoided as it can increase the risk of liver toxicity.

In Female Children, in Female Adolescents and Women of Childbearing Potential and Pregnant Women: Orfiril long must be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Orfiril long should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses during pregnancy.

Combined Therapy: When starting Orfiril long in patients already on other anticonvulsants, these should be tapered slowly: initiation of Orfiril long therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, eg phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have

been withdrawn it may be possible to maintain seizure control on a reduced dose of Orfiril long. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Administration: Orfiril long Enteric Coated Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight. Orfiril long tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

Orfiril long Chrono Controlled Release tablets are for oral administration.

Orfiril long Chrono is a prolonged release formulation of Orfiril long which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Orfiril long Chrono may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.

Daily dosage requirements vary according to age and body weight.

In patients where adequate control has been achieved Orfiril long Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

In view of the sustained release process and the nature of the excipients in the formula, the inert matrix of the granules is not absorbed by the digestive tract. It is eliminated in the stools after the active substances have been released.

Orfiril long Syrup is for oral administration.

Daily dosage requirements vary according to age and body weight. Orfiril long Syrup may be given twice daily. If it is necessary to dilute Orfiril long Syrup, the

recommended diluent is Syrup BP, but syrup containing SO2 as a preservative should not be used. The diluted product will have a 14-day shelf life. Orfiril long

Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

ORFIRIL LONG INTERACTIONS

Effects of Valproate on Other Drugs: Neuroleptics, MAO Inhibitors, Antidepressants and Benzodiazepines: Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

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

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

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

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

Lamotrigine: Orfiril long 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.

Zidovudine: Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Olanzapine: Orfiril long acid may decrease the olanzapine plasma concentration.

Rufinamide: Orfiril long acid may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of Orfiril long acid. Caution should be exercised, in particular in children, as this effect is larger in this population.
Vitamin K-Dependent Anticoagulants: The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by Orfiril long acid. The prothrombin time should be closely monitored.

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

Effects of Other Drugs on Valproate: Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease Orfiril long acid plasma concentrations. Dosages should be adjusted according to blood levels in case of combined therapy. On the other hand, combination of felbamate and Orfiril long may increase Orfiril long acid plasma concentration. Orfiril long dosage should be monitored. Orfiril long acid metabolite serum levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

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

In case of concomitant use of valproate and highly protein bound agents (e.g. aspirin), free Orfiril long acid plasma levels may be increased.

Orfiril long acid 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: Decrease in Orfiril long acid blood level, sometimes associated with convulsions, has been observed when imipenem or meropenem were combined. If these antibiotics have

to be administered, close monitoring of Orfiril long acid blood levels is recommended.

Cholestyramine may decrease the absorption of Orfiril long.

Rifampicin may decrease the Orfiril long acid 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 such as lopinavir, ritonivar decrease valproate plasma level when co-administered.

Other Interactions: Caution is advised when using Orfiril long in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at risk patients such as those with preexisting encephalopathy.
Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

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

ORFIRIL LONG SIDE EFFECTS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Hepatic failure
- Birth defects
- Decreased IQ following in utero exposure
- Pancreatitis
- Hyperammonemic encephalopathy
- Suicidal behavior and ideation
- Bleeding and other hematopoietic disorders
- Hypothermia
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reactions
- Somnolence in the elderly

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Mania

The incidence of treatment-emergent events has been ascertained based on combined data from two three week placebo-controlled clinical trials of Orfiril long in the treatment of manic episodes associated with bipolar disorder. The adverse reactions were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, Orfiril long, and lithium carbonate. A total of 4%, 8% and 11% of patients discontinued therapy due to intolerance in the placebo, Orfiril long, and lithium carbonate groups, respectively.

Table 2 summarizes those adverse reactions reported for patients in these trials where the incidence rate in the Depakote-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the Depakote-treated group was statistically significantly greater than the placebo group. Vomiting was the only reaction
that was reported by significantly ($p \leq 0.05$) more patients compared to placebo.

The following additional adverse reactions were reported by greater than 1% but not more than 5% of the 89 Depakote-treated patients in controlled clinical trials:
Body as a Whole: Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.

Cardiovascular System: Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.

Digestive System: Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.

Hemic and Lymphatic System: Ecchymosis.

Metabolic and Nutritional Disorders: Edema, peripheral edema.

Musculoskeletal System: Arthralgia, arthrosis, leg cramps, twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.

Respiratory System: Dyspnea, rhinitis.

Skin and Appendages: Alopecia, discoid lupus erythematosus, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses: Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus.

Urogenital System: Dysmenorrhea, dysuria, urinary incontinence.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, Orfiril long was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the Depakote-treated patients (6%), compared to 1% of placebo-treated patients.

Table 3 lists treatment-emergent adverse reactions which were report Depakote-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to Orfiril long alone, or the combination of Orfiril long and other antiepilepsy drugs.

Table 4 lists treatment-emergent adverse reactions which were report patients in the high dose valproate group, and for which the incidence was greater than in the low dose group, in a controlled trial of Orfiril long monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse reactions can be ascribed to Orfiril long alone, or the combination of valproate and other antiepilepsy drugs.

The following additional adverse reactions were reported by greater than 1% but less than 5% of the 358 patients treated with valproate in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.

Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.

Skin and Appendages: Rash, pruritus, dry skin.

Special Senses: Taste perversion, abnormal vision, deafness, otitis media.

Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Migraine

Based on two placebo-controlled clinical trials and their long term extension, valproate was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Of the 202 patients exposed to valproate in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long term extension study, the adverse reactions reported as
the primary reason for discontinuation-treatedby≥patients1%ofwere248 valp
alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 5 includes those adverse reactions reported for patients in the placebo-controlled trials where the incidence rate in the Depakote-treated group was greater than 5% and was greater than that for placebo patients.

The following additional adverse reactions were reported by greater than 1% but not more than 5% of the 202 Depakote-treated patients in the controlled clinical trials:
Body as a Whole: Chest pain, chills, face edema, fever and malaise.

Cardiovascular System: Vasodilatation.

Digestive System: Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.

Hemic and Lymphatic System: Ecchymosis.

Metabolic and Nutritional Disorders: Peripheral edema, SGOT increase, and SGPT increase.

Musculoskeletal System: Leg cramps and myalgia.

Nervous System: Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.

Respiratory System: Cough increased, dyspnea, rhinitis, and sinusitis.

Skin and Appendages: Pruritus and rash.

Special Senses: Conjunctivitis, ear disorder, taste perversion, and tinnitus.

Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Orfiril long. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic: Hair texture changes, hair color changes, photosensitivity, erythema multiforme, toxic epidermal necrolysis, nail and nail bed disorders, and Stevens-Johnson syndrome.

Psychiatric: Emotional upset, psychosis, aggression, psychomotor hyperactivity, hostility, disturbance in attention, learning disorder, and behavioral deterioration.

Neurologic: There have been several reports of acute or subacute cognitive decline and behavioral changes (apathy or irritability) with cerebral pseudoatrophy on imaging associated with valproate therapy; both the cognitive/behavioral changes and cerebral pseudoatrophy reversed partially or fully after valproate discontinuation.

Musculoskeletal: Fractures, decreased bone mineral density, osteopenia, osteoporosis, and weakness.
Hematologic: Relative lymphocytosis, macrocytosis, leucopenia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Endocrine: Irregular menses, secondary amenorrhea, hyperandrogenism, hirsutism, elevated testosterone level, breast enlargement, galactorrhea, parotid gland swelling, polycystic ovary disease, decreased carnitine concentrations, hyponatremia, hyperglycinemia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Metabolism and nutrition: Weight gain.

Reproductive: Aspermia, azoospermia, decreased sperm count, decreased spermatozoa motility, male infertility, and abnormal spermatozoa morphology.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss.

Other: Allergic reaction, anaphylaxis, developmental delay, bone pain, bradycardia, and cutaneous vasculitis.

ORFIRIL LONG CONTRAINDICATIONS

- Orfiril long should not be administered to patients with hepatic disease or significant hepatic dysfunction.
- Orfiril long is contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase-Huttenlocherγ(POLG;Syndrome).g., Alper and children under two years of age who are suspected of having a POLG-related disorder.
- Orfiril long is contraindicated in patients with known hypersensitivity to the drug.
- Orfiril long is contraindicated in patients with known urea cycle disorders.

- Orfiril long is contraindicated for use in prophylaxis of migraine headaches in pregnant women.

ORFIRIL LONG PREGNANCY

Orfiril long Epitome Life Sciences is contraindicated during pregnancy and lactation.

If necessary using this medication during lactation it should solve the issue of termination of breastfeeding. Category effects on the fetus by FDA - C.

ORFIRIL LONG OVERDOSE

Cases of accidental and deliberate valproate overdosage 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.
Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times 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.

Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the valproate formulations may lead to hypernatremia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully. 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.

ORFIRIL LONG PRECAUTIONS

Orfiril long acid inhibits platelet aggregation and therefore, the risk of prolonged bleeding exists. In patients receiving valproate and undergoing surgery, the potential

for bleeding complications should be assessed. In addition, any patient receiving valproate for a long time and developing spontaneous bruise and bleeding should be prevented immediately from further valproate therapy. The therapy can be continued after the blood picture returns to normal.

Valproate can lead to drug-induced pancreatitis usually within 6 months of treatment. Patients with acute pain in the abdomen while receiving valproate should undergo thorough laboratory investigations to rule out pancreatitis. In the event of causal relation, Orfiril long should be discontinued and substituted with another antiepileptic drug.

Liver dysfunction, liver failure during valproate therapy is particularly common in children of epilepsy who also have other congenital metabolic or degenerative disease, organic brain disease and mental retardation. In the presence of symptoms eg, sudden onset of loss of seizure control, severe weakness, lethargy, edema, vomiting and jaundice, Orfiril long should be withdrawn immediately.

Use in pregnancy & lactation: The incidence of neural tube defects in children born to women with epilepsy both treated as well as untreated including those treated with valproate is in the region of 0.7-1% and folic acid supplementation during pregnancy is known to reduce this risk. In the absence of appropriate and rigorously controlled clinical trials addressing this question, the women of childbearing potential should be told of the risks and benefits of receiving antiepileptic therapy, including valproate, during pregnancy. The lowest effective dose should be used and the fetus should be
examined *in utero* for congenital abnormalities using-fetoproteinultrasoundat a regular intervals throughout pregnancy.

Use in children: Orfiril long is not suitable for children <20 kg.