150225172013

Valproex C.R. 500 mg

Controlled -Release Scored Tablets

Generic name: valproic acid / Sodium valproate

Composition:

Active ingredients: Sodium Valproate 333 mg, Valproic acid 145 mg Corresponding to 500 mg sodium valproate.

Inactive ingredients:

Magnesium stearate, silicon dioxide, methacrylate copolymer, ethylcellulose, hypermellose, talc, saccharin, titanium dioxide, polyethylene glycol.

WARNING: LIFE-THREATENING ADVERSE REACTIONS

Hepatotoxicity Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Valproex is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months.

Teratogenicity Valproate can produce teratogenic effects such as neural tube defects (eg. spina bifida). Accordingly, the use of Valproex in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (eg. migraine) is contemplated.

Pancreatitis Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Warning: Antiepileptic drugs (AEDs), increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/ or any unusual changes in mood or behaviour.

Clinical Particulars **Therapeutic indications** Treatment of generalised, partial or other epilepsy.

Acute treatment of manic episodes associated with bipolar disorder Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures Prophylaxis of migraine headaches

Posology and method of administration: Valproex Controlled Release Scored Tablets are for oral administration. Valproex CR tablets can be divided. Valproex is a prolonged release formulation which reduces peak concentration and ensures more even plasma concentrations throughout the day. Valproex may be given once or twice daily. Daily dosage requirements vary according to age and body weight.

DOSAGE & ADMINISTRATION

Mania Valproex CR tablets are administered orally. The recommended initial dose is 25 mg/ kg/ day given once daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In a placebo-controlled clinical trial of acute mania or mixed type, patients were dosed to a clinical response with a trough plasma concentration between 85 and 125 mcg/ml. the maximum recommended dosage is 60 mg/kg/day. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no data to support the benefits of Valproex in such longer-term treatment. i.e. beyond 3 weeks.

Epilepsy Valproex CR tablets are administered orally, and can be divided. As Valproex dosage is titrated upward, concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected.

Complex Partial Seizures ***For adults and children 10 years of age or older.*** Monotherapy (Initial Therapy)

Valproate has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 - 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of Valproex therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy Valproex may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in 2 to 3 doses. In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy.

Simple and Complex Absence Seizures The recommended initial dose is 15 mg/kg/day, increasing at 1-week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in 2 to 3 doses. A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures are considered to range from 50 to 100 mcg/mL. Some patients may be controlled with lower or higher serum concentrations. As Valproex dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected. Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In epileptic patients previously receiving Depakene therapy, Valproex should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on Valproex, a dosing schedule of 2 or 3 times a day may be elected in selected patients.

Migraine Valproex are administered orally, and can be divided. The recommended starting dose is 500 mg once daily or divided into 250 mg twice daily for one week. Some patients may benefit from doses up to 1000 mg/day. In clinical trials, there was no evidence that higher doses led to greater efficacy.

General Dosing Advice

Dosing in Elderly Patients Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response.

Dose-Related Adverse Reactions

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose- related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥135 mcg/mL (males). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

G.I. Irritation Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

Contraindications
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

Special warnings and precautions for use 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.

Special warnings See boxed warning above

Liver 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 anticonvulsant therapy, are infants and in particular young children under the age of 3 years 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 years, 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 due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). Monotherapy is recommended in children under the age of 3 years when prescribing Valproex, but the potential benefit of Valproex should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy

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:

- 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 family for children) 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 therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most 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 decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Valproex 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, Valproex should be discontinued. Women of childbearing potential: This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Valproex is prescribed for the first time, or when a women of child bearing potential treated with Valproex plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Suicidal ideation and behaviour: Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do 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.

Carbapenem agents: The concomitant use of valproate and carbapenem agents is not recommended.

Precautions *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.

Renal insufficiency: In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of valproates, the potential benefit of Valproex should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Valproex.

Weight gain: valproates 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.

Pregnancy: Women of childbearing potential should not be started on Valproex without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus.

Diabetic patients: Valproex is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Alcohol: Alcohol intake is not recommended during treatment with valproate

Interaction with other medicinal products and other forms of interaction ***Effects of Valproex on other drugs***

- *Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines:* Valproex may potentiate the effect of other psychotropics such asantipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the 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:* Valproex has no effect on serum lithium levels
- *Phenobarbital:* Valproex 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:* Valproex 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:* Valproex decreases phenytoin total plasma concentration. Moreover Valproex 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:* Valproex 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%.
- *Zidovudine:* Valproex may raise zidovudine plasma concentration leading to increased zidovudine toxicity.
- *Vitamin K-dependent anticoagulants:* The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.
- *Temozolomide:* Co-administration of temozolomide and Valproex may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Valproex Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy. On the other hand, combination of felbamate and Valproex decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Valproex dosage should be monitored. Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Valproex may need adjustment. In case of concomitant use of Valproex and highly protein bound agents (e.g. aspirin), free valproic acid plasma levels may be increased. Valproic 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: 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. If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed. Colestyramine may decrease the absorption of Valproex.. Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

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

Concomitant administration of valproate and topiramate 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 pre-existing encephalopathy. Valproex usually has no enzyme-inducing effect; as a consequence, Valproex does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception, including the oral contraceptive pill.

Pregnancy and lactation See boxed warning

Women of childbearing potential should not be started on Valproex without specialist neurological advice.

Adequate counselling should be made available to all women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus. Women who are taking Valproex and who may become pregnant should receive specialist neurological advice and the benefits of its use should be weighed against the risks. Valproex is the antiepileptic of choice in patients with certain types of epilepsy such as generalised epilepsy ± myoclonus/photosensitivity. For partial epilepsy, Valproex should be used only in patients resistant to other treatment.

If pregnancy is planned, consideration should be given to cessation of Valproex treatment, if appropriate.

When Valproex treatment is deemed necessary, precautions to minimize the potential teratogenic risk should be followed.

Pregnancy *- Risk associated with epilepsy and antiepileptics* In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the overall rate of malformations has been demonstrated to be higher than the rate (approximately 3 %) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy. Malformations most frequently encountered are cleft lip and cardio-vascular malformations. No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. Antiepileptic drugs should be withdrawn under specialist supervision.

- Risk associated with seizures

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.

- Risk associated with valproate In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. There is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.

In humans: Available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Data have suggested an association between in-utero exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy. Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy. Autism spectrum disorders have also been reported in children exposed to valproate in utero.

- In view of the above data The following recommendations should be taken into consideration: This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before Valproex is prescribed for the first time, or when a women of child bearing potential treated with Valproex plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Valproex during pregnancy. If a woman plans a pregnancy or becomes pregnant, Valproex therapy should be reassessed whatever the indication:

- In epilepsy, valproate therapy should not be discontinued without reassessment of the benefit/risk. If further to a careful evaluation of the risks and benefits, Valproex treatment is to be continued during pregnancy, it is recommended to use Valproex in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.
- In addition, if appropriate, folate supplementation should be started before pregnancy at relevant dosage (5mg daily) as it may minimise the risk of neural tube defects.
- Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defects or other malformations.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate.

- Risk in the neonate Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Valproex during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs. 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 the pregnancy.

Lactation Excretion of valproates in breast milk is low, with a concentration between 1 % to 10 % of total maternal serum levels. Although there appears to be no contra-indication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Valproex, specifically haematological disorders.

Effects on ability to drive and use machines Use of Valproex may provide seizure control such that the patient may be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

Undesirable effects See boxed warning

Congenital and familial/genetic disorders: Hepato-biliary disorders: rare cases of liver injury. Severe liver damage, including hepatic failure sometimes resulting in death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient. Gastrointestinal disorders (nausea, gastralgia, diarrhoea) frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Valproex with or after food or by using Enteric Coated Valproex. Very rare cases of pancreatitis, sometimes lethal, have been reported.

Nervous system disorders: Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage. Very rare cases of extrapyramidal symptoms which may not be reversible including reversible parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported. Dose-related ataxia and fine postural tremor have occasionally been reported.

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

Psychiatric disorder: Confusion has been reported

Metabolic disorders: Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Valproex should be discontinued. Very rare cases of hyponatraemia have been reported. Syndrome of inappropriate secretion of ADH (SIADH) Hyperammonaemia associated with neurological symptoms has also been reported . In such cases further investigations should be considered.

Blood and lymphatic system disorders: Frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia. The blood picture returned to normal when the drug was discontinued. Bone marrow failure, including pure red cell aplasia, Agranulocytosis.

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 (Valproex has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.

Skin and subcutaneous tissue disorders: Rash rarely occurs with Valproex. In very rare cases toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported. Transient hair loss, which may sometimes be dose-related, has often been reported. Regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Reproductive system and breast disorders: Amenorrhoea and dysmenorrhea have been reported. Very rarely gynaecomastia has occurred. Male infertility.

Vascular disorders: The occurrence of vasculitis has occasionally been reported.

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

Renal and urinary disorders: There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), but the mode of action is as yet unclear. Very rare cases of enuresis have been reported.

Immune system disorders: Angioedema, Drug Rash with Eosinophilia, Systemic Symptoms (DRESS) syndrome and allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

General disorders: Very rare cases of non-severe peripheral oedema have been reported.

Increase in weight may also occur. Weight gain being a risk factor for polycystic ovary syndrome, it should be carefully monitored.

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. 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. 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. 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.

PHARMACOLOGICAL PROPERTIES *Pharmacodynamic properties* Sodium valproate and valproic acid are anticonvulsants.

The most likely mode of action for Valproex is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA. In certain in-vitro studies it was reported that Valproex could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Valproex does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Valproex 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.

Pharmacokinetic properties The half-life of valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children. In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels. The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological (or therapeutic) effects of Valproex may not be clearly correlated with the total or free (unbound) plasma valproic acid levels. In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of valproate make the measurement of plasma levels less dependent upon time of sampling.

Shelf life 24 months.

Special precautions for storage Valproex is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place at temperature not exceeding 30°C.

Package and storage

Package Carton box contains 3 laminated aluminum (Al / PVC /OPA) / hard aluminum blisters each of 10 film coated tablets and inner leaflet.
Carton box contains 5 laminated aluminum (Al / PVC /OPA) / hard aluminum blisters each of 6 film coated tablets and inner leaflet.

Storage Store at a temperature not exceeding 30°C, in dry place and do not exceed the expiry date indicated on the outer package.

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فالبرويكس سى آر ٥٠٠ مجم

أقراص مغلفة ممتدة المفعول قابلة للانقسام

الاسم العلمى: حامض فالبرويك/صوديوم فالبروات

تحذير: أعراض جانبية خطيرة قد تؤدى إلى الوفاة

التسمم الكبدى: حدثت حالات من الفشل الكبدى المؤدية إلى الوفاة فى بعض المرضى اللذين تناولوا حامض الفالبرويك ومشتقاته. الأطفال تحت سن سنتين معرضين لنسبة خطر مرتفعة لحدوث التسمم الكبدى المؤدى إلى الوفاة ، خصوصاً هؤلاء المرضى الذين يتعاطون أكثر من دواء مضاد للتشنجات والذين يعانون من اضطرابات الأيض الخلقية والذين يعانون من تشنجات شديدة مصحوبة بتأخر عقلى وكذلك الذين يعانون من أمراض عضوية بالمخ. ولذلك فعند وصف هذا الدواء (فالبرويكس) لمثل هؤلاء المرضى يجب ممارسة الحذر الشديد واستخدامه كعلاج منفرد (بدون أى أدوية أخرى). يجب مراعاة توازن الفائدة المرجوة من هذا العلاج مقابل احتمالات المخاطرة. إن احتمالية حدوث حالات التسمم الكبدى تقل بدرجة كبيرة فى المرضى الأكبر سناً.

إن احتمالية حدوث هذا العرض تكون فى الستة أشهر الأولى من تعاطى الدواء. إن حدوث تسمم كبدى خطير أو مهدد للحياة قد يسبقه أعراض غير مميزة مثل الشعور بالضيق، والضعف والخمول وتورم فى الوجه وفقدان الشهية والتقيؤ. فى المرضى الذين يعانون من الصرع ربما يحدث فقدان السيطرة على التشنجات أيضاً. يجب مراقبة المرضى عن كثب لظهور هذه الأعراض. وينبغى إجراء اختبارات وظائف الكبد قبل العلاج وذلك على فترات متكررة، وخصوصاً خلال الـ ٦ أشهر الأولى.

تشوهات الأجنة: يمكن أن يحدث فالبروات آثاراً مشوهة مثل عيوب الأنبوب العصبى (مثل الشوكة المشقوقة). تبعاً لذلك، فإن استخدام النساء اللائى لديهن احتمالات للإنجاب يتطلب مراعاة توازن الفائدة المرجوة من هذا العلاج مقابل احتمالات المخاطرة بإصابة الجنين. هذا مهم بشكل خاص عند التفكير فى علاج الحالات التى يمكن أن تتماثل للشفاء بشكل عفوى والتى لا ترتبط عادة مع إصابة دائمة أو خطر الموت (الصداع النصفى مثلاً).

التهاب البنكرياس: تم الإبلاغ عن حالات التهاب بنكرياس مهددة للحياة فى كل من الأطفال والبالغين ممن تلقوا علاج فالبروات. وقد وصفت بعض الحالات بالنزفية مع التدهور السريع من الأعراض الأولية إلى الموت. وقد تم الإبلاغ عن حالات الاستخدام بعد فترة وجيزة، وكذلك بعد عدة سنوات من الاستخدام. يجب تحذير المرضى وأولياء أمورهم أن آلام البطن والغثيان والتقيؤ و / أو فقدان الشهية يمكن أن يكون أعراض التهاب البنكرياس التى تتطلب تقييم طبى فورى. إذا تم تشخيص التهاب البنكرياس، ينبغى التوقف عن العلاج بالفالبروات فوراً وينبغى الشروع فى العلاج البديل للحالة الطبية الأساسية على النحو المطلوب.

تحذير: أدوية الصرع تزيد من خطر الأفكار أو السلوك الانتحارى فى المرضى الذين يتناولون هذه الأدوية لأى عرض. يجب مراقبة المرضى الذين يتم علاجهم بأدوية الصرع لرصد أى إشارة أو تفاقم للاكتئاب، أفكار انتحارية، سلوك انتحارى أو أى تغييرات غير عادية فى المزاج أو السلوك.

قم بقراءة كل هذه النشرة بعناية قبل البدء بتناول هذا الدواء

- ينصح بالحفاظ على هذه النشرة، فقد تحتاج إلى قراءتها مرة أخرى.
- إذا كان لديك أى أسئلة أخرى ، اسأل الطبيب أو الصيدلى
- لقد تم وصف هذا الدواء لك، فلا تمرره إلى الآخرين، فقد يضرهم، حتى لو كان عندهم نفس الأعراض.
- إذا حصل أياً من الأعراض الجانبية بصورة خطيرة، أو إذا لاحظت أى آثار جانبية غير مدرجة فى هذه النشرة، يرجى إخبار الطبيب أو الصيدلى

محتوى هذه النشرة: ١. ما هو فالبرويكس سى آر ٥٠٠ مجم وما هى استخداماته.
٢. قبل أخذ فالبرويكس سى آر ٥٠٠ مجم.
٣. كيفية أخذ فالبرويكس سى آر ٥٠٠ مجم.
٤. الأعراض الجانبية المحتملة.
٥. كيفية تخزين فالبرويكس سى آر ٥٠٠ مجم.
٦. مزيد من المعلومات.

١. ما هو فالبرويكس سى آر ٥٠٠ مجم وما هى استخداماته: إن اسم المستحضر فالبرويكس "سى آر" يعنى أن أقراص هذا المستحضر هى ممتدة المفعول أو بمعنى آخر أن المادتين الفعالتين - فالبروات صوديوم و حامض فالبرويك يتم انطلاقهم من القرص ببطء على فترة معينة من الوقت. إن المادتين ينتميان إلى مجموعة من الأدوية تسمى مضادات الصرع أو مضادات التشنجات ويعملان عن طريق تهدئة المخ. إن مستحضر فالبرويكس سى آر ٥٠٠ مجم يستخدم لعلاج الصرع والتشنجات والصداع النصفى وبعض الحالات النفسية طبقاً لوصف الطبيب.

٢. قبل أخذ فالبرويكس سى آر ٥٠٠ مجم: لا تأخذ فالبرويكس سى آر ٥٠٠ مجم فى الحالات الآتية:

*إذا كنت تعانى من الحساسية من المواد الفعالة (فالبروات الصوديوم وحمض الفالبرويك) أو من أى من المواد الغير فعالة (أنظر رقم ٦. مزيد من المعلومات).

*أعراض الحساسية تشمل طفح جلدى وصعوبة فى البلع أو التنفس وتورم الشفاة أو الوجه أو اللسان.

*إذا كان لديك مشاكل فى الكبد أو كنت أنت أو كانت عائلتك لديها تاريخ مشاكل فى الكبد.

*إذا كان لديك مرض نادر يسمى البورفيريا.

لا تأخذ هذا الدواء إذا كان أى مما ذكر أعلاه ينطبق عليك.

إذا كنت غير متأكد، تحدث إلى الطبيب أو الصيدلى قبل تناول الدواء.

يلاحظ بشكل خاص عند العلاج بمستحضر فالبرويكس: أن عدد قليل من الناس ممن يتناولون فالبروات الصوديوم لعلاج الصرع تأتيهم أفكار إيذاء أو قتل لأنفسهم. إذا كان لديك هذه الأفكار فى أى وقت اتصل بطبيبك على الفور.

تحقق مع الطبيب أو الصيدلى قبل تناول هذا الدواء فى الحالات التالية:

- إذا كان لديك مرض السكر فهذا الدواء قد يؤثر على نتائج اختبارات البول.
- إذا كان لديك مشاكل فى الكلى عندئذ قد يعطيك طبيبك جرعة أقل.
- إذا كان لديك نوبات (الصرع)، أو أمراض الدماغ أو حالات أيضية تؤثر على الدماغ.
- إذا كان لديك "اضطراب دورة اليوريا" حيث يتراكم غاز الأمونيا فى الجسم بكثرة.