PROPOSED PACKAGE INSERT

SCHEDULING STATUS **S3**

PROPRIETARY NAMES (AND DOSAGE FORMS)

EPROLEP CR 200 (film-coated tablets)

EPROLEP CR 300 (film-coated tablets)

EPROLEP CR 500 (film-coated tablets)

COMPOSITION

Active ingredients

EPROLEP CR 200: Each film-coated controlled release tablet contains 133,2 mg sodium valproate and 58,0 mg valproic acid, together equivalent to 200 mg sodium valproate.

EPROLEP CR 300: Each film-coated controlled release tablet contains 199,8 mg sodium valproate and 87,0 mg valproic acid, together equivalent to 300 mg sodium valproate.

EPROLEP CR 500: Each film-coated controlled release tablet contains 333,0 mg sodium valproate and 145,0 mg valproic acid, together equivalent to 500 mg sodium valproate.

Inactive ingredients

Hypromellose, acesulfame potassium, colloidal hydrate silica, sodium laurylsulphate, dibutyl sebacate, basic butylated methacrylate copolymer, magnesium stearate, titanium dioxide.

EPROLEP CR 200, 300 & 500 are sugar free.

EPROLEP CR 200, 300 & 500 contains 2,40, 3,60 and 6,00 mg acesulfame potassium respectively.

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Anticonvulsants, including antiepileptics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Valproate is an antiepileptic which produces an increase in the level of gamma-aminobutyric acid (GABA) in the brain.

Pharmacokinetic properties

Valproate is absorbed rapidly and completely after oral administration.

Peak plasma concentration is observed in 1 to 4 hours, although this can be delayed if given with food. The apparent volume of distribution is about 0,2 litre/kg. Its extent of binding to plasma proteins is usually about 90 %, but the fraction bound is reduced as the total concentration of valproate is increased through the therapeutic range.

Valproate (95 %) undergoes hepatic metabolism, with less than 5 % excreted unchanged in urine. Its hepatic metabolism occurs mainly by UGT enzymes and ß-oxidation.

Valproate is a substrate for CYP2C9 and CYP2C19, but metabolism by these enzymes accounts for a relatively minor portion of its elimination. Some of the medicine metabolites, notably 2-propyl-2-pentenoic acid and 2-propyl-4-pentenoic acid, are nearly as potent antiseizure agents as the parent compound; however, only the former (2-en-valproic acid) accumulates in plasma and brain to a potentially significant extent.

Sodium valproate is mainly excreted in urine following metabolism via glucuro-conjugation and beta-oxidation.

The half-life of valproate is approximately 15 hours but is reduced in patients taking other antiepileptic medicines. It is usually shorter in children.

Renal impairment

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 in epilepsy is between 30 and 100 µg/mℓ. This range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels.

The pharmacological (or therapeutic) effects of sodium valproate are not clearly correlated with the total or free (unbound) plasma valproic acid levels.

In cases where measurement of plasma levels is considered necessary, trough plasma levels should be used for therapeutic monitoring.

INDICATIONS

- The treatment of generalised epilepsy, particularly with the following patterns of seizures:
    - absence
    - myoclonic
    - tonic-clonic
    - atonic
    - mixed

  as well as, for partial epilepsy:
    - simple or complex seizures
    - secondary generalised seizures
    - specific syndromes (West, Lennox-Gastaut).
- For the treatment and prevention of mania associated with bipolar disorders.

CONTRA-INDICATIONS

- Hypersensitivity to sodium valproate or any of the ingredients of **EPROLEP CR**.
- Pre-existing liver disease or a family history of severe hepatic dysfunction.
- Urea cycle disorders (hyperammonemic encephalopathy)**.**
- Concurrent use with MOAI (see **INTERACTIONS**).
- Porphyria.
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

Severe liver damage

Cases of severe liver damage, resulting in fatalities have been reported.

Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy are infants and young children under the age of 3 with severe disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease. After the age of 3, the incidence of occurrence is reduced and decrease with age. In most cases, such liver damage occurred during the first 6 months of therapy.

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):

- non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain;
- in patients with epilepsy, recurrence of seizures.

Patients (or their family for children) should be instructed to report immediately any such signs to their doctor should they occur. Investigations including clinical examination and biological assessment of the liver function should be undertaken immediately.

Detection

Liver function tests should be performed before and then periodically monitored during the first 6 months of therapy. Amongst usual investigations, tests, which reflect protein synthesis, particularly prothrombin rate, are most relevant. An adjustment of dosage may be considered when appropriate and tests should be repeated as necessary. 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 **EPROLEP CR** therapy. As a matter of precaution and

in case they are taken concomitantly, salicylates should also be discontinued, since they use the same metabolic pathway.

Pancreatitis

Severe pancreatitis, which may result in fatalities, has been reported. Young children are at particular risk. This risk is decreased with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, **EPROLEP CR** should be discontinued.

Women of childbearing potential

See **PREGNANCY AND LACTATION** for information on foetal malformations and developmental problems in children exposed to valproate (as in **EPROLEP CR**) *in utero,* **EPROLEP CR** should not be used in young girls and women of child-bearing potential, or during pregnancy and lactation (see **CONTRA-INDICATIONS**). When other treatments are ineffective or not tolerated, see "**Recommendations to consider in girls reaching puberty and women who can have children**" under **PREGNANCY AND LACTATION**.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with **EPROLEP CR** in several indications. Patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

Special precautions

Liver function

Liver function tests should be carried out before therapy (see **CONTRA-INDICATIONS**), and periodically during the first 6 months especially in patients at risk (see **WARNINGS**).

More extensive biological investigation (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Blood tests

Blood tests (blood cell count, including platelet count, bleeding time and coagulation test) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see **SIDE-EFFECTS**).

Renal impairment

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 **Pharmacokinetics**).

Autoimmune disease

Although immune disorders have been infrequently noted during the use of **EPROLEP CR**, the potential benefit of **EPROLEP CR** should be weighed against the risk in patients with systemic lupus erythematosus.

Diabetic patients

EPROLEP CR is eliminated mainly through the kidney, partly in the form of ketone bodies, and this may give false-positive readings in the urine testing of possible diabetics.

Other disorders

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

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 **Side effects**). Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome.

Elderly patients (65 years or older)

Elderly patients tend to have increased free, unbound valproate concentrations and lowered intrinsic clearances, indicating a reduction of valproate metabolising capacity and a fall in serum albumin. These patients may also be more susceptible to certain adverse reactions, including somnolence. Therefore, these patients should receive a lower daily dosage, and the serum concentrations should be kept in the lower therapeutic range.

Dental

Valproate (contained in **EPROLEP CR**) inhibits the secondary phase of platelet aggregation, which may be reflected in prolonged bleeding time and/or frank haemorrhaging. In addition, the leukopenic and thrombocytopenic effects of valproate may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work, whenever possible, should be deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss and toothpicks.

Surgical

Because of the thrombocytopenic effects of valproate, as well as its inhibition of the secondary phase of platelet aggregation and production of abnormal coagulation parameters (e.g., low fibrinogen), monitoring of platelet counts and coagulation tests are recommended in patients prior to scheduled surgery.

Ability to drive or use machines

Patients should be warned of the risk of somnolence with **EPROLEP CR**; the more so in cases of anticonvulsant polytherapy or association with benzodiazepines (see **INTERACTIONS** and **SIDE EFFECTS**).

INTERACTIONS

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Effects of EPROLEP CR on other medicines

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

EPROLEP CR may potentiate the effect of other psychotropic agents such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines. Patients should be monitored and the dosage should be adjusted when appropriate.

Phenobarbital

EPROLEP CR increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Clinical monitoring is recommended right through the first 15 days of combined treatment. Phenobarbital doses should immediately be reduced if sedation occurs and phenobarbital plasma levels determined when appropriate.

Primidone

EPROLEP CR increases primidone plasma levels, thereby aggravating its adverse effects (such as sedation). These symptoms usually cease with long-term treatment. Clinical monitoring is recommended, especially at the beginning of combined therapy, with dosage adjustment when appropriate.

Phenytoin

EPROLEP CR decreases phenytoin total plasma concentration. Moreover **EPROLEP CR** increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Clinical monitoring is consequently recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

Carbamazepine

EPROLEP CR, co-administered with carbamazepine may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended, especially at the beginning of combined therapy; dosage adjustment should be applied when appropriate.

Lamotrigine

EPROLEP CR may reduce lamotrigine metabolism and increase its mean half-life; the lamotrigine dosage should be decreased when appropriate. The risk of rash may possibly be increased by co-administration of lamotrigine with **EPROLEP CR.**

Zidovudine

EPROLEP CR may raise zidovudine plasma concentration, which may result in an increase in zidovudine toxicity.

Effects of other medicines on EPROLEP CR

By lowering the seizure threshold, antidepressants and neuroleptics may antagonise the antiepileptic activity of **EPROLEP CR** and may require **EPROLEP CR** dosage adjustments.

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels where combined therapy is used.

Co-administration of felbamate and **EPROLEP CR** may increase valproate serum concentration. **EPROLEP CR** dosage should be adjusted where required.

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy. Chloroquine may also lower the seizure threshold.

During concomitant use of **EPROLEP CR** and highly protein bound agents (aspirin), valproate free serum levels may be increased.

Close monitoring of INR should be performed in case of concomitant use of vitamin K dependent factor anticoagulants (e.g. warfarin) because the anticoagulant effect of these agents may be increased due to displacement from plasma protein binding sites by **EPROLEP CR.**

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

Carbapenem antibiotics (imipenem/meropenem/ertapenem): Decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

Cholestyramine may decrease the absorption of **EPROLEP CR**.

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, dosage adjustments of **EPROLEP CR** may be necessary when it is co-administered with rifampicin.

Other interactions

EPROLEP CR usually has no enzyme inducing effect; consequently **EPROLEP CR** does not reduce efficacy of oestrogen- and/or progestogen- containing medicines in women receiving hormonal contraception.

PREGNANCY AND LACTATION

EPROLEP CR should not be used in pregnancy and lactation (see **CONTRA-INDICATIONS**).

Pregnancy

Malformations

There have been reports of foetal abnormalities in women receiving valproate during the first trimester. An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects hypospadias, malformation of the limbs and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate (as contained in **EPROLEP CR**). Malformations most frequently encountered are cleft lip and cardio-vascular malformations. The incidence of neural tube defects in women taking **EPROLEP CR** during first trimester has been estimated to be in the region of 1 %.

Developmental problems

Developmental problems have been reported in up to 30 to 40 % of pre-school children exposed to valproate (as contained in **EPROLEP CR**) in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

Children exposed to valproate in the womb are also at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).

Other risks in the neonate

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken **EPROLEP CR** during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors; afibrinogenemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other antiepileptic enzyme inducing medicines.

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.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Hepatic failure, resulting in the death of a newborn and of an infant have been reported following the use of valproate during pregnancy.

Recommendations to consider in girls reaching puberty and women who can have children:

- **EPROLEP CR** should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Only prescribe valproate medicines (such as **EPROLEP CR**) if other treatments are ineffective or not tolerated.
- Inform patients of the risks of taking **EPROLEP CR** during pregnancy.
- Advise patients taking **EPROLEP CR** about effective contraception during their treatment.
- Inform patients to urgently consult their doctor in the case of planning a pregnancy, or if pregnancy is suspected.

- Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and, if indicated, amniocentesis.
- **EPROLEP CR** treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- Women and girls who have been prescribed **EPROLEP CR** should not stop taking their medicines without consulting their doctor as doing so could result in harm to themselves or to an unborn child.
- Inform patients about the need for regular medical checks during treatment.
- Regularly review the need for treatment and re-assess the balance of the benefits and risks for female patients taking valproate and for girls reaching puberty.

Lactation

Valproate is distributed into breast milk. Concentrations in breast milk have been reported to be 1 to 10 % of the total maternal serum concentration. See **CONTRA-INDICATIONS**.

DOSAGE AND DIRECTIONS FOR USE

EPROLEP CR may be taken with food to reduce gastro-intestinal side effects.

EPROLEP CR 200, 300 and **500** tablets are intended for oral administration.

The tablets should be swallowed whole, if necessary with a little water (but not with aerated mineral water) and not crushed or chewed.

EPROLEP CR is a controlled release formulation of **EPROLEP CR**, which reduces peak concentration and ensures a more even plasma concentration throughout the day. **EPROLEP CR** may be given once or twice daily.

Daily dosage requirements vary according to age and body mass.

In patients where adequate control has been achieved, **EPROLEP CR** formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Adult dose

Epilepsy

Dosage should start at 600 mg/day, where applicable in divided doses, increasing by 200 mg/day at three day intervals until control is achieved; this is generally within the range of 1 000 to 2 000 mg/day (i.e. 20 – 30 mg/kg body mass).

If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day, or one other antiepileptic agent may be added at a low dosage.

In patients already receiving other therapy, the same pattern should be followed. If increased sedation is observed, dosage of barbiturates or benzodiazepines (e.g. lorazepam) should be reduced as that of **EPROLEP CR** is increased; dosage of both **EPROLEP CR** and other agents should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with **EPROLEP CR** alone.

Treatment and prevention of mania associated with bipolar disorders

The recommended initial dose is 1 000 mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effect.

Doses should be adjusted according to individual clinical response.

Prophylactic treatment should be established individually with the lowest effective dose.

Elderly patients (65 years and older)

Although the pharmacokinetics of **EPROLEP CR** is modified in the elderly, this is of 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 medicine is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Elderly patients have lowered intrinsic clearances, indicating a reduction of valproate metabolising capacity and a fall in serum albumin. These patients may also be more susceptible to certain adverse reactions, including somnolence. Therefore, these patients should receive a lower daily dosage, and the serum concentrations should be kept in the lower therapeutic range.

Renal insufficiency

It may be necessary to decrease the dosage. The dosage should be adjusted according to clinical monitoring, since plasma concentrations may be misleading (see **Pharmacokinetics**).

Combined therapy

When starting **EPROLEP CR** in patients already on other anticonvulsants, these should be tapered slowly. Initiation of **EPROLEP CR** therapy should then be gradual, with target dose being reached after about 2 weeks.

In certain cases it may be necessary to increase the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants that induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine.

Once known enzyme inducers have been withdrawn, or if side effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of **EPROLEP CR**. When barbiturates are being administered concomitantly and particularly if sedation is observed, the dosage of barbiturate should be reduced.

General considerations

The concentration of valproate in plasma that appears to be associated with therapeutic effects is approximately 30 - 100 µg/mℓ . 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 (see **Pharmacokinetics**).

SIDE EFFECTS

The following side effects have been observed during treatment with **EPROLEP CR**:

Blood and lymphatic system disorders

Frequent: Anaemia, thrombocytopenia (see **WARNINGS AND SPECIAL PRECAUTIONS** – "**Blood tests**").

Less frequent: Platelet aggregation inhibition or thrombocytopenia, reversible prolongation of bleeding time, bone marrow depression, red cell hyperplasia and leucopenia, isolated reduction of fibrinogen pancytopenia, agranulocytosis, anaemia macrocytic, macrocytosis.

Immune system disorders

Less frequent: Allergic reactions, angioedema.

Endocrine disorders

Less frequent: Life-threatening pancreatitis. Plasma amylase should be measured if there is acute abdominal pain, hyperglycaemia, syndrome of inappropriate secretion of ADH (SIADH), hypothyroidism.

Metabolism and nutrition disorders

Frequent: Hyponatraemia.

Frequency unknown: Hyperammonaemic encephalopathy in patients with urea cycle disorders, hyperglycinaemia.

Psychiatric disorders

Frequent: Amnesia, sleep disorders, primarily insomnia, nervousness, somnolence, emotional lability, confusional state, aggression[1].

Less frequent: Behavioural, mood or mental changes, abnormal dreams, agitation, anxiety, confusion, depression, drowsiness, hallucinations, thinking abnormalities, unusual excitement, restlessness, irritability, sedation,

[1] Mainly observed in the paediatric population

lethargy, encephalopathy, coma, reversible dementia associated with cerebral atrophy, aggression, hyperactivity, learning disorder.

Nervous system disorders

Frequent: Ataxia, extrapyramidal disorder, stupor, convulsion, memory impairment, trembling of hands and arms, tremor, headache, dizziness.

Less frequent: Abnormal gait, encephalopathy, lethargy, reversible parkinsonism, ataxia, catatonic reaction, dysarthria, hypertonia, hypokinesia, paraesthesia, increased reflexes, speech disorder, tardive dyskinesia, twitching, increased alertness.

Eye disorders

Frequent: Amblyopia.

Less frequent: Nystagmus, spots before eyes, diplopia, conjunctivitis, dry eyes, eye pain.

Ear and labyrinth disorders

Frequent: Tinnitus deafness.

Less frequent: Otitis media, vertigo, ear disorder or pain.

Cardiac disorders

Less frequent: Palpitations, tachycardia.

Vascular disorders

Less frequent: Hypotension, hypertension, postural hypotension, vasodilation.

Respiratory, thoracic and mediastinal disorders

Frequent: Pharyngitis, flu syndrome.

Less frequent: Dyspnoea, pneumonia, bronchitis, epistaxis, increased cough, rhinitis, sinusitis, pleural effusion.

Gastro-intestinal disorders

Frequent: Abdominal or stomach cramps, diarrhoea, dyspepsia, nausea and vomiting, indigestion.

Less frequent: Hematemesis, periodontal abscess, anorexia or increase in appetite, constipation, dry mouth, faecal incontinence, flatulence, gastroenteritis, glossitis, stomatitis, taste perversion, minor gastric irritation.

Hepato-biliary disorders

Frequency unknown: Hepatic failure resulting in death has occurred in patients taking **EPROLEP CR**. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, vomiting, jaundice and oedema.

Hepatotoxicity, liver dysfunction.

Skin and subcutaneous tissue disorders

Frequent: Alopecia, skin rash.

Less frequent: Discoid lupus erythematosus, dry skin, ecchymosis, furunculosis, petechia, pruritus, hirsutism, acne, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders

Frequent: Back pain.

Less frequent: Leg cramps, malaise, neck pain, neck rigidity, arthralgia, arthrosis, hypertonia, myalgia, myasthenia, bone mineral density decreased, osteopenia, osteoporosis, fractures in patients on long-term treatment with **EPROLEP CR**.

Renal and urinary disorders

Less frequent: Urinary incontinence, cystitis, dysuria, reversible defects in renal tubular function (Franconi's syndrome), enuresis.

Reproductive system and breast disorders

Frequent: Change in menstrual periods.

Less frequent: Vaginal haemorrhage, amenorrhoea, dysmenorrhoea, metrorrhagia, vaginitis, gynaecomastia.

General disorders and administration site disorders

Frequent: Infections, asthenia.

Less frequent: Peripheral oedema (swelling), fatigue, unusual weight gain or loss, fever, chest pain, chills, oedema, malaise.

Congenital and familial/genetic disorders

Frequency unknown: See ***"Malformations"*** and ***"Developmental problems***" under **PREGNANCY AND LACTATION**.

Investigations

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

Frequency unknown: **Diagnostic tests**

Metyrapone test: decreased response to metyrapone.

Thyroid function test: decreased T_4 and free T_3 and T_4 concentrations.

Urine ketone test: false-positive results.

Physiology/laboratory test values

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) and Lactate dehydrogenase (LDH): minor elevations of serum concentrations occur frequently and appear to be dose related; elevations may indicate asymptomatic hepatotoxicity.

Amino acid screening: increases in glycine may occur.

Bilirubin: serum concentrations may be increased; increase may indicate potentially serious hepatotoxicity.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Symptoms of overdose may be serious CNS depression and respiration may be impaired.

Full recovery is usual following treatment.

Treatment

Treatment of overdose consist primarily of supportive and symptomatic measures.

To decrease absorption – The effectiveness of emesis or gastric lavage will depend upon the time elapsed since ingestion.

To enhance elimination – Haemodialysis, or tandem haemodialysis and haemoperfusion, may result in significant reductions in valproate serum concentrations.

Specific treatment – Maintenance of adequate urinary output must be ensured. Naloxone has been administered to counteract severe CNS depression, but it also theoretically reverses the anticonvulsant effect and should be used with caution.

Supportive care – Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

IDENTIFICATION

EPROLEP CR 200: White oval film-coated tablets with dimensions of approximately 13,8 mm x 7,2 mm.

EPROLEP CR 300: White oblong film-coated tablets with dimensions of approximately 16,7 mm x 6,7 mm and with a break mark on both sides.

EPROLEP CR 500: White oblong film-coated tablets with dimensions of approximately 17,7 mm x 9,2 mm and with a break mark on both sides.

PRESENTATION

EPROLEP CR tablets are packed in packs of 56 or 100 tablets in blisters made of silver oPA/Al/PVC foil and Aluminium push-through foil, in a cardboard carton. Not all pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store in the original packaging (keep blisters in the carton in order to protect from light and moisture) at or below 25 °C.

KEEP MEDICINE OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

EPROLEP CR 200: 45/2.5/0412

EPROLEP CR 300: 45/2.5/0093

EPROLEP CR 500: 45/2.5/0094

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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