Epilim™

Sodium Valproate BP
Valproic Acid BP

50028

PRESENTATION
Epilim CHRONO 200 Tablet: White, round, biconvex, film coated tablet. Each film coated controlled release tablet contains Sodium Valproate BP 133.2 mg and Valproic Acid BP 58 mg (equivalent to sodium valproate 200 mg)
Epilim CHRONO 300 Tablet: White, round, biconvex, film coated tablet. Each film coated controlled release tablet contains Sodium Valproate BP 199.8 mg and Valproic Acid BP 87 mg (equivalent to sodium valproate BP 300 mg)
Epilim CHRONO 500 Tablet: White, oblong shaped, film coated tablet. Each film coated controlled release tablet contains Sodium Valproate BP 333 mg and Valproic Acid BP 145 mg (equivalent to sodium valproate BP 500 mg)
Epilim Syrup: Clear red coloured syrupy liquid with Cherry flavour. Each 5ml of syrup contains Sodium Valproate BP 200 mg.

DESCRIPTION
Active ingredient: Sodium valproate and valproic Acid

INDICATIONS
Epilepsy: For the treatment of generalized, partial or other epilepsy, with the following pattern seizures: Absence, Myoclonic, Tonic clonic, Atonic, Mixed. As well as, for partial epilepsy: Simple or complex seizures, Secondary generalized seizures, Specific syndromes (West, Lennox-Gastaut).
Mania: For the treatment of manic episodes of bipolar disorders.
Other: Prophylaxis of migraine headaches.

DOSAGE AND ADMINISTRATION
Daily dosage should be established according to age and body weight; nevertheless the wide individual sensitivity to valproate should be also considered.
A good correlation has not been established between daily dose, serum concentration and therapeutic effect and optimum dosage should be determined essentially according to the clinical response; the determination of valproic acid plasma levels may be considered in addition to clinical monitoring when adequate seizure control is not achieved or when adverse effects are suspected. The reported effective range is usually between 40-100 mg/L (300-700 mol/L).

Initiation of Epilim/ Epilim CHRONO therapy (oral administration) :
• In patients without other antiepileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 days interval in order to reach the optimum dosage in about one week.
• In patients previously receiving antiepileptic agents, substitution with Epilim/ Epilim CHRONO should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered then stopped.
• Addition of another antiepileptic agent should be done progressively where it is necessary (see "Drug interactions").

Oral administration of Epilim/ Epilim CHRONO : practical considerations
Dosage
Initial daily dosage is usually 10-15 mg/kg, then doses are titrated up to the optimum dosage (see "Initiation of Epilim/Epilim CHRONO therapy").
This is generally within the range 20-30 mg/kg. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased *.adequately; patients should be carefully monitored when receiving daily doses higher than 50 mg/kg (see "Precautions")
• In children, usual dosage is about 30 mg/kg per day.
• In adults, usual dosage is within the range 20-30 mg/kg per day.
• In elderly, although the pharmacokinetics of Epilim CHRONO are modified, they have limited clinical significance and dosage should be determined by seizure control.

Migraine prophylaxis: The recommended starting dose is 500mg/day for a week, thereafter increasing to 1000mg/day. Efficacy and safety in migraine prophylaxis in subject below 12 years and above 65 years have been established.

SPECIAL POPULATIONS

Children
Epilepsy Indication
Among the oral pharmaceutical forms, the following formulation is more appropriate for administration to children less than 11 years (syrup).

Bipolar Indication
In children and adolescents:
The safety and efficacy of Epilim/ Epilim CHRONO for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.
Elderly
(See Dosage)
Hepatic Impairment
(See Contraindication, Warning and Precaution)
Renal Impairment
(See Precaution)

Female children, women of childbearing potential and pregnant women
Epilim/ Epilim CHRONO must be initiated and supervised by a specialist, experienced in the management of epilepsy or bipolar disorder.Valproate should not be used in female children and women of childbearing potential other treatments are ineffective or not tolerated (See Contraindication, Warning, Pregnancy). Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (PPP Section 5). In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, Epilim should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose of non-prolonged release formulations should be divided into at least two single doses during pregnancy.Preferably Epilim CHRONO / Epilim 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 atleast two single doses during pregnancy.

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives.
However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

ADMINISTRATION
Enteric coated tablets, liquid and syrup may be given twice daily.
The use of a sustained release form (Epilim CHRONO) allows to give the drug once daily.
Epilim CHRONO may be used in children provided that they are able to take such a form. The breakable forms of Epilim CHRONO allow a fine dose adjustement.

CONTRA-INDICATIONS
Epilim/Epilim Chrono is contraindicated in the following situations:

Treatment of epilepsy
• in pregnancy unless there is no suitable alternative treatment (see warning and pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see warning and pregnancy).

Treatment of bipolar disorder
• in pregnancy (see warning and pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see warning and pregnancy).

All indications
- Hypersensitivity to Epilim/Epilim CHRONO
- Acute or chronic hepatitis
- Personal or family history of severe hepatitis, especially drug related
- Hepatic porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG, e.g. Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having a POLG-related disorder (see warnings)
-Patients with known urea cycle disorders (see precautions)

WARNINGS
Pregnancy Prevention Program
Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders(See Pregnancy).

Epilim/Epilim Chrono is contraindicated in the following situations:

Treatment of epilepsy
• in pregnancy unless there is no suitable alternative treatment (see contraindications and pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see contraindications and pregnancy).

Treatment of bipolar disorder
• in pregnancy (see contraindications and pregnancy).
• in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see contraindications and pregnancy).

Conditions of Pregnancy Prevention Program:
The prescriber must ensure that
• Individual circumstances are evaluated in each case and discussed with the patient. This is to guarantee the patient's engagement and understanding of the therapeutic options together with the risks and the measures needed to mitigate the risks.
• the potential for pregnancy is assessed for all female patients.
• the patient understands and acknowledges the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
• the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
• the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (see subsection contraception of this warning), without interruption during the entire duration of treatment with valproate.
• the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders.
• the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
• the patient understands the need to urgently consult her physician in case of pregnancy.
• the patient has received the patient guide.
• the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).
These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.
Pharmacist or other health care professional (to be adapted locally) must ensure that
• the patient card is provided with every valproate dispensing and that the patients understand its content.
• the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Female children
• The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
• The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero.
• In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention program should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test
Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user-independent form such as an intra-uterine device or implant) **or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.**

Annual treatment reviews by a specialist
The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning.
For the epilepsy indication, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 8). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.
For the bipolar disorder indication, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology>/ pre-natal **medicine for evaluation and counselling regarding the exposed pregnancy (see Pregnancy).**

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention program. A patient guide and patient card should be provided to all women of childbearing potential using valproate.
A risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist, and when a woman is planning a pregnancy or is pregnant.

Severe liver damage
Conditions of occurence :
Severe liver damage resulting sometimes in fatalities have been exceptionally 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 seizure 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 significantly reduced and progressively decreases 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 "Conditions of occurence"):
- 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 a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection :
Liver function should be periodically monitored during the first 6 months of therapy. 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 Epilim CHRONO 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.

Pancreatitis
Severe pancreatitis which may result in fatalities have been very rarely reported. Young children are at particular risk but this risk decreased with increasing age. Severe cases, with 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, valproate should be discontinued.

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives.
However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

Suicidal ideation and behavior
Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo valproate controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this effect is not known. Therefore, patients should be monitored for signs of suicidal ideation and behavior, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately if signs of suicidal ideation or behavior emerge.

Carbapenems agents
The concomitant use of valproate and carbapenem agents is not recommended.
Patients with known or suspected mitochondrial disease:
Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear - encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG; e.g. Alpers-Huttenlocher Syndrome). POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to un-explained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

Aggravated convulsions
As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.

Liver function tests
Liver function tests should be carried out before therapy (see "Contraindications and special warnings"), and periodically during the first 6 months especially in patients at risk (see "Warnings"). As with most antiepileptic drugs, increased liver enzymes may be noted, particularly at the beginning of the therapy ; they are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients ; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Hematological tests
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.

Patients with systemic lupus erythematosus
Although immune disorders have been only exceptionally noted during the use of Epilim/Epilim CHRONO, the potential benefit of Epilim/Epilim CHRONO should be weighed against its potential risk in patients with systemic lupus erythematosus.

Urea cycle disorders
When an urea cycle enzymatic deficiency is suspected, ammonemia should be assessed prior to treatment because of the risk of hyperammonemia with valproate.

Weight gain
Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise the risk.

Carnitine palmitoyl transferase (CPT) type II deficiency
Patients with an underlying carnitine palmitoyl transferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate.

Alcohol
Alcohol intake is not recommended during treatment with valproate

Children
Monotherapy is recommended in children under the age of 3 years when prescribing Epilim/Epilim CHRONO, but the potential benefit of Epilim/Epilim CHRONO should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see "Warnings").
The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.

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.

INTERACTIONS
1)Effects of Valproate on other drugs
Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines
Epilim/ Epilim CHRONO may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines.

Lithium
Epilim/ Epilim CHRONO has no effect on serum lithium levels.

Phenobarbital
Epilim/Epilim CHRONO increases phenobarbital plasma concentrations and sedation may occur, particularly in children.

Primidone
Epilim/ Epilim CHRONO increases primidone plasma levels with exacerbation of its adverse effects (such as sedation) ; these signs cease with long-term treatment.

Phenytoin
Epilim/Epilim CHRONO increases phenytoin total plasma concentration.

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

Lamotrigine
Epilim/Epilim CHRONO 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 increase zidovudine toxicity.

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

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

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

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

Nimodipine
Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %.

2) Effects of other drugs on Valproate
Antiepileptics
Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.
On the other hand, combination of felbamate and valproate decreases valproic acid clearance by 22% to 50%, and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.
Valproic acid metabolites 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
Mefloquine increases valproic acid metabolism and has a convulsant effect ; therefore epileptic seizures may occur in cases of combined therapy.

Highly protein bound agents
In case of concomitant use of valproate and highly protein binded agents (aspirin), valproic acid free serum levels may be increased.

Vitamin K dependent factor anticoagulant
Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

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

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

Rifampicin
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 ritampicin.**

Protease inhibitors
Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co administered.

Cholestyramine
Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

Estrogen-containing products
Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control), when adding, or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels.
Valproate usually has no enzyme inducing effect; as a consequence, **valproate does not reduce efficacy of oestroprogestative agents** in women receiving hormonal contraception.

Other interactions
Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia.

Quetiapine
Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

PREGNANCY

Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled.

Teratogenicity and Developmental Effects
Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy including other antiepileptics, are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.
In animals: teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations
Data from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.
Available data show an increased incidence of minor or major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.
There are limited data on the long term outcomes.
Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorders (approximately three-fold), and childhood autism (approximately five-fold) compared with the general population.
Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

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

For the bipolar disorder indication, if a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered.

Pregnant women
Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see Contraindications and warnings).
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:
• Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> / prenatal medicine **for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation** (5 mg daily) **before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.**

Risk in the neonate
Exceptional cases of haemorragic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This haemorragic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decrease in other coagulation factors; afibrinaemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin-K dependant factors induced by phenobarbital and enzymatic inducers.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of the pregnancy.
Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

Estrogen-containing products
Valproate does not reduce efficacy of hormonal contraceptives.
However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

LACTATION :
Excretion of valproate in breast milk is low, with a concentration between 1 % to 10 % of maternal serum levels. Based on literature and clinical experience, breast feeding can be envisaged, taking into account the EPILIM CHRONO / EPILIM safety profile, especially hematological disorders.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
The patient should be warned of the **risk of somnolence** especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:
Very common ≥10%; Common ≥1% and <10%; Uncommon ≥0.1 and <1%;
Rare ≥0.01 and <0.1%; Very rare <0.01%, Unknown (cannot be estimated from available data).
Congenital, familial and genetic disorders (see Pregnancy)

Blood and lymphatic system disorders
Common: **anaemia, thrombocytopenia** (see Precautions).
Uncommon: **pancytopenia, leucopenia.**
Rare: **bone marrow failure,** including **pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.**

Investigations
Rare: **coagulation factors decreased** (at least one), **abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged)** (see Precautions and Pregnancy). **biotin deficiency/biotinidase deficiency.**

Nervous system disorders
Very common: **tremor**
Common: **extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness (for intravenous injection, dizziness may occur within a few minutes and** it usually resolves spontaneously within a few minutes**),**
Uncommon: **coma*, encephalopathy*, lethargy*, reversible Parkinsonism, ataxia, paresthesia, Aggravated convulsions.**
Rare: **reversible dementia associated with reversible cerebral atrophy, cognitive disorder .**

***Stupor and lethargy sometimes leading to transient coma / encephalopathy they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy and they decreased on withdrawal of treatment or reduction of dosage. These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in valproate doses.**

Eye disorders
Not known: **diplopia**

Ear and labyrinth disorders
Common: **deafness.**

Respiratory, thoracic and mediastinal disorders
Uncommon: **pleural effusion.**

Gastrointestinal disorders
Very common: **nausea.**
Common: **vomiting, gingival disorder** (mainly **gingival hyperplasia), stomatitis , upper abdominal pain, diarrhea**
Uncommon: **pancreatitis, sometimes lethal** (see Precautions).

Renal and urinary disorders
Common: **urinary incontinence**
Uncommon: **renal failure**
Rare: **enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome**

Skin and subcutaneous tissue disorders
Common: **hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders.**
Uncommon: **angioedema, rash, hair disorder** (such as **hair texture abnormal, hair colour changes, hair growth abnormal**),
Rare: **toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.**

Musculoskeletal and connective tissues disorders
Uncommon: **bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim CHRONO / Epilim.**
Rare: **systemic lupus erythematosus, rhabdomyolysis** (see Precautions).

Endocrine disorders
Uncommon: **Syndrome of Inappropriate Secretion of ADH (SIADH) hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased).**
Rare: **hypothyroidism** (see Section Pregnancy).

Metabolism and nutrition disorders
Common: **hyponatraemia, weight increased*.**
***Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see Precaution).**
Rare: **hyperammonaemia** (see Precaution), **obesity*.**
***Cases of isolated and moderate hyperammonemia without change in liver function tests may occur and should not** cause **treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered** (see Precaution).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: **myelodysplastic syndrome.**

Vascular disorders
Common: **haemorrhage** (see Precaution and Pregnancy).
Uncommon: **vasculitis.**

General disorders and administration site conditions
Common: **hypothermia , peripheral non-severe oedema.**

Hepatobiliary disorders
Common: **liver injury** (see Warnings).

Reproductive system and breast disorders
Common: **dysmenorrhea.**
Uncommon: **amenorrhea**
Rare: **male infertility, polycystic ovaries**

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

OVERDOSAGE
Signs of acute massive overdosage usually include a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock.
Deaths have occurred following massive overdose; nevertheless, a favourable outcome is usual.
Symptoms may however be variable and **seizures have been reported in the presence of very high plasma levels. Cases of hypertension intracranial related to cerebral edema have been reported.**
The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose.

SPECIAL PRECAUTIONS FOR STORAGE
- Epilim CHRONO tablets must be kept in their own protective foil, in a dry place, at room temperature (below 30°C).
- Liquid and syrup should be stored at room temperature and away from direct sunlight.
- Keep out of reach of the Children.

Package Quantities:
Epilim CHRONO 200 Tablet: Box of 6 x 10 x 200mg in Blister Packs.
Epilim CHRONO 300 Tablet: Box of 6 x 10 x 300mg in Blister Packs.
Epilim CHRONO 500 Tablet: Box of 8 x 6 x 500mg in Blister Packs.
Epilim Syrup: Bottle of 100ml Syrup.

Manufactured by:
synovia
Synovia Pharma PLC., Station Road, Tongi, Gazipur.
Under License From **Sanofi, France.** 546628

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Direction Slip artwork legend

Product Name	:	Epilim
Code number	:	546628
CDCS Version	:	03
Dimension	:	L 32 x W 13.5 inches
Min. size of text	:	8 pt
Used Colors	:	Black C ■ Rad ■