NAME OF THE MEDICINAL PRODUCT
Epilim Chrono 500 Controlled Release

QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Constituents
Each tablet contains 333mg Sodium Valproate and 145mg Valproic Acid equivalent to 500mg sodium valproate.
Excipients with known effect:
Sodium 46.08 mg (see Special Warnings and Precautions for Use).

PHARMACEUTICAL FORM
Prolonged Release Tablet.

PRODUCT DESCRIPTION
Oblong, practically white, scored film-coated tablets

INDICATIONS
Treatment of generalized or partial 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 generalized seizures
- Specific syndromes (West, Lennox-Gastaut)

Treatment and prevention of mania associated with bipolar disorder.

DOSAGE AND METHOD OF ADMINISTRATION
Epilim Chrono Controlled Release Tablets are for oral administration.
Epilim Chrono is a prolonged release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.
Epilim Chrono 500 may be given once or twice daily. The tablets should be swallowed whole and not crushed or chewed.
Daily dosage requirements vary according to age and body weight.
In patients where adequate control has been achieved Epilim Chrono formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage
Usual requirements are as follows:
Adults
Dosage should start at 600mg daily increasing by 200mg at three-day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20- 30mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg
Initial dosage should be 500mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day.
Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg
An alternative formulation of Epilim should be used in this group of patients, due to the tablet size and need for dose titration. Epilim Syrup is an alternative.

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

Elderly

Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control.

The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency

It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see *Pharmacokinetic Properties*).

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see *Special Warnings and Precautions for Use and Undesirable Effects*).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see *Contraindications and Special Warnings and Precautions for Use*).

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Epilim, concomitant use in children under 3 years can increase the risk of liver toxicity (see *Special warnings*).

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unlessother treatments are ineffective or not tolerated (see *Special warnings and precautions for use* and *Fertility, pregnancy and lactation*).The benefit and risk should be carefully reconsidered at regular treatment reviews. Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Combined Therapy

When starting Epilim in patients already on other anti-convulsants, these should be tapered slowly; initiation of Epilim therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, eg phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

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

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

In treatment and prevention of mania associated with bipolar disorders:

Adults

The recommended initial dose is 1000mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effects.

The recommended maintenance dosage for the treatment of bipolar disorder is between 1000mg and 2000mg daily. In exceptional cases, the dose may be increased to not more than 3000mg daily. Doses should be adjusted according to individual clinical response.

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

CONTRAINDICATIONS

Epilim is contraindicated in the following situations:

- ***Treatment of epilepsy***

- in pregnancy unless there is no suitable alternative treatment (see Section Warnings/Precautions and section Pregnancy)
- in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Section Warnings/Precautions and section Pregnancy)

- ***Treatment of bipolar disorder***

- in pregnancy (see Section Warnings/Precautions and section Pregnancy)
- in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Section Warnings/Precautions and section Pregnancy)

- ***All indications***
  - Hypersensitivity to sodium valproate
  - Acute or chronic hepatitis
  - Patient 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 Section Warnings/Precautions)
  - Patients with known urea cycle disorders (see Section Warnings/Precautions)
  - Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see Section Warnings/Precautions - Patients at risk of hypocarnitinemia)

WARNINGS/PRECAUTIONS

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 Section Pregnancy)

Epilim is contraindicated in the following situations:

Treatment of Epilepsy

- In pregnancy unless there is no suitable alternative treatment (See Section Contraindications and Section Pregnancy).
- In women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled. (See Section Contraindications and Section Pregnancy).

Treatment of bipolar disorder

- In pregnancy (See Section Contraindications and Section Pregnancy).
- In women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled. (See Section Contraindications and Section Pregnancy).

<u>Conditions of Pregnancy Prevention Program:</u>

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 and acknowledges the risk of lower weight at birth for the

gestational age for children exposed to valproate *in utero* (see section Pregnancy).

- 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.

Pharmacists or other healthcare professionals 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:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The 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.* The prescriber must also inform them about the risk of lower weight at birth for the gestational age.
- In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention program should be discussed. Every effort should be made by the specialist to switch 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 childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare 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 review at least annually 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 Pregnancy). 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 prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see Section Pregnancy).

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorization 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.

An 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.

Use in male patients of reproductive potential

A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy).

Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception.

The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for

healthcare professionals and male patients. A patient guide and a patient card should be provided to all men of reproductive potential using valproate.

Severe liver damage

Conditions of occurrence:

Severe liver damage resulting sometimes in fatalities, has exceptionally been reported.

Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see Section Warnings/Precautions) or degenerative disease.

After the age of 3 years, the risk is significantly reduced and it 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 above: *'Conditions of occurrence'*):

- 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 laboratory assessment of liver functions should be undertaken immediately.

Detection:

Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy, especially in patients at risk (see also Section Interactions). Among the 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 therapy. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they follow the same metabolic pathway.

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 the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see Contraindications).

Urea cycle disorders and risk of hyperammonemia:

When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Epilim (see Section Contrindications and Warnings/Precautions - Patients at risk of hypocarnitinemia and Severe liver damage).

Patients at risk of hypocarnitinemia

Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in

hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also Warnings on Patients with known or suspected mitochondrial disease and urea cycle disorders and risk of hyperammonemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

Patients should be warned to report immediately any signs of hyperammonemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed.

Patients with known systemic primary carnitine deficiency and corrected for hypocarnitinemia should be treated with valproate only if the benefits of valproate treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinemia should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Carnitine supplementation should be considered in these patients.

See also Sections Interactions, Adverse Reactions and Overdose.

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been very rarely reported. Young children are at particular risk; but this risk decreases with increasing age. Severe seizures, neurological impairment or anti-convulsant 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.

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 randomized placebo 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 should signs of suicidal ideation or behavior emerge.

Severe Cutaneous Adverse Reactions and Angioedema

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case signs of SCARs or angioedema are observed, prompt assessment is needed and treatment must be discontinued if diagnosis of SCARs or angioedema is confirmed.

Carbapenem agents:

The concomitant use of valproate and carbapenem agents is not recommended (See Section Interactions).

Aggravated convulsions

As with other anti-epileptic 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.

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 serum valproate levels (see Section Interactions).

Liver function tests

Liver function tests should be carried out before therapy (see Section Contraindications), and periodically during the first 6 months especially in patients at risk (see Section Warnings/Precautions and see also Section Interactions). As with most antiepileptic drugs, a slight increase in 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) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see Section Adverse Reactions).

Patients with systemic lupus erythematosus:

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

Weight gain:

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 minimize the risk (see Section Adverse Reactions).

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, but the potential benefit of Epilim should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see Section Warnings/Precautions and see also Section Interactions).

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity.

Renal insufficiency:

It may be necessary to decrease the dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

INTERACTION

Effects of valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

  Epilim may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage should be adjusted when appropriate.

- ***Lithium***

  Epilim has no effect on serum lithium levels

- ***Phenobarbital***

Epilim 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***

Epilim 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 a combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Epilim decreases phenytoin total plasma concentration. Moreover, Epilim increases the phenytoin free form with possible overdose 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 co-administered with carbamazepine as valproate may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Epilim reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increase lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

- ***Zidovudine***

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

- ***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 levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

- ***Propofol***

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

- ***Nimodipine***

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

Effects of other drugs on valproate

- ***Anti-epileptics***

Anti-epileptics with enzyme inducing effect (including *phenytoin, phenobarbital, carbamazepine*) decrease valproic acid serum 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 valproate decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.

Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or

phenobarbital. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

- ***Mefloquine***
Mefloquine increases valproic acid metabolism and has a convulsing 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 bound agents (aspirin), valproic acid free serum levels may be increased.

- ***Vitamin K-dependent factor anti-coagulant***
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, imipenem 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 stabilized on valproic acid should be avoided (see section Warnings/Precautions). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels 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 rifampicin.

- ***Protease inhibitors***
Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma levels when co-administered.

- ***Cholestyramine***
Cholestyramine may lead to a decrease in the 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 estroprogestative agents in women receiving hormonal contraception.

- ***Metamizole***
Metamizole may decrease serum valproate levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring serum valproate levels as appropriate.

- ***Methotrexate***
Some case reports describe a significant decrease in serum valproate levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring serum valproate levels as appropriate.

<u>Other interactions</u>

Risk of liver damage
The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see Section Warnings/Precautions - “Severe liver damage” and “children”).
Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see Section Warnings/Precautions - “Severe liver damage” and “children”).
In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see Section Warnings/Precautions).

Topiramate and acetazolamide
Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

Pivalate-conjugated medicines
Concomitant administration of valproate and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see Section 5 Patients at risk of hypocarnitinemia). Concomitant administration of these medicines with valproate is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

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

REPRODUCTION
Pregnancy

Treatment of epilepsy
- Valproate is contraindicated during pregnancy, unless there is no suitable alternative treatment.
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see Contraindications and Warnings/Precautions).

Treatment of bipolar disorder
- Valproate is contraindicated during pregnancy.
- Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see Contraindications and Warnings/Precautions).

Teratogenicity and developmental effects from female and male exposure
Valproate was shown to cross the placental barrier both in animal species and in humans (see Section Pharmacokinetics).

Pregnancy Exposure Risk related to valproate
In females, both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate..

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see Section Carcinogenicity).

Risk to children of fathers treated with valproate

A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam.

The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07).

Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see Warnings/Precautions).

Congenital malformations from in utero exposure

A meta-analysis (including registries and cohort studies) showed that about 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2-3%). The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic polytherapy including valproate is higher than that of anti-epileptic drugs polytherapy not including valproate. This risk is dose-dependent in valproate monotherapy, and available data suggest it is dose-dependent in valproate polytherapy. However, 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 and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment / loss due to ear and/or nose malformations (secondary effect) and/or direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neurodevelopmental disorders from in utero exposure

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to mothers with untreated epilepsy. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, 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 anti-epileptics. 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 from a study conducted using registries in Denmark show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.
Available data from a second study conducted using registries in Denmark show that children exposed to valproate *in utero* are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

Lower weight at birth for the gestational age from in utero exposure
In utero exposure to valproate can lead to a lower weight at birth for the gestational age.
In preclinical studies a dose-related fetal weight decrease was demonstrated in animals exposed to valproate *in utero* compared to unexposed animals (see section Reproductive and developmental toxicity).
Epidemiological studies have reported a decrease in mean birth weight, and higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate *in utero* in comparison to unexposed or lamotrigine-exposed children.
Available data in human do not allow to conclude on a potential dose-related effect.

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/Precautions). 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 Section Contraindications and Warnings/Precautions).
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 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.

<u>Risk in the neonate</u>

- Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors, afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers.
- Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycemia 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.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of the 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 serum valproate levels (see Section Interactions).

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, breastfeeding can be envisaged, taking into account the Epilim safety profile, especially hematological disorders (see Section Adverse Reactions).

Fertility

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see Section Adverse Reactions). Valproate administration may also impair fertility in men (see Section Adverse Reactions). In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

The patient should be warned of the risk of somnolence especially in cases of anti- convulsant polytherapy or association with benzodiazepines (see Section Interactions).

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/ 10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from available data).

Congenital, familial and genetic disorders: (see Section Pregnancy)

Blood and lymphatic system disorders:

Common: anemia, thrombocytopenia, (see Section Warnings/Precautions). Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anemia 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 Section Warnings/Precautions and Section 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* (see below), 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, abdominal pain upper, diarrhea frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing treatment.
*Also observed a few minutes after intravenous injection with spontaneous resolution within a few minutes.

Uncommon: pancreatitis, sometimes lethal, (see Section Warnings/Precautions).

Renal and urinary disorders:
Common: urinary incontinence.
Uncommon: renal failure.

Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome but the mode of action is as yet unclear.

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 color changes, hair growth abnormal)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Not known: hyperpigmentation

Musculoskeletal and connective tissue disorders:

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis (see Warnings/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: hyponatremia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section Warnings/Precautions).

Rare: hyperammonemia* (see Section Warnings/Precautions), 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 Section Warnings/Precautions - Urea cycle disorders and risk of hyperammonemia and patients at risk of hypocarnitinemia).

Not known: hypocarnitinemia (see Sections Contraindications and Warnings/Precautions).

Neoplasms benign, malignant and unspecified (including cysts and polyps):
Rare: myelodysplastic syndrome.
Not known: acquired Pelger–Huet anomaly.

Vascular disorders:

Common: hemorrhage (see Section Warnings/Precautions and Section Pregnancy).

Uncommon: vasculitis.

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe oedema peripheral.

Hepatobiliary disorders:

Common: liver injury (see Section Warnings/Precautions*).*

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 behavior*, psychomotor hyperactivity*, learning disorder*
*These ADRs are principally observed in the pediatric population.

Pediatric population
The safety profile of valproate in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section Warnings/Precautions). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

OVERDOSE

Signs and Symptoms

Signs of acute massive overdose, 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 favorable outcome is usual.

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 edema have been reported.

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

Management

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

In case of valproate overdose resulting in hyperammonemia, carnitine can be given through IV route to attempt to normalize ammonia levels.

Naloxone has been successfully used in a few isolated cases.

In case of massive overdose, hemodialysis and hemoperfusion have been used successfully.

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST

Since valproate is excreted mainly through the kidney partly in the forms of ketone bodies, ketone body excretion test may give false positive results in diabetic patients.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Anti-epileptics, ATC Code: N03AG01

The most likely mode of action for Epilim 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 Epilim could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV infected subjects show that Epilim does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Epilim 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.

Pharmacokinetics

The reported effective therapeutic range for plasma valproic acid levels is 40- 100mg/L (278-694 µmol/L). This reported range may depend on time of sampling and presence of co-medication.

Distribution

The percentage of free (unbound) drug is usually between 6-15% of the 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 Epilim may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see section Pregnancy)

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism

The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

Elimination

The half-life of Epilim is usually reported to be within the range 8 – 20 hours. Based on limited data from literature, an approximate 20% increase in valproate clearance has been reported in some patients that were concomitantly treated with valproate and estrogen-containing products, which may result in a decrease in serum valproate levels (see Section Interactions). Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction. Based on published literature, in pediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults. In children aged 2-10 years, valproate clearance is 50% higher than in adults. Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

NONCLINICAL SAFETY DATA

Genotoxicity

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay) and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown.

Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus patients with untreated epilepsy, provided contradictory results. The biological significance of an increase in SCE frequency is not known.

Carcinogenocity

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

Reproductive and developmental toxicity

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits.

In mice, rats, and rabbits, *in utero* exposure to valproate induced a dose-related decrease in fetal weight, intra-uterine growth restriction and reduction in crown rump length compared to unexposed animals.

In published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive

performance.
In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to pediatric population is unknown.

PHARMACEUTICAL PARTICULARS

Incompatibilities
None.

Shelf life: 36 months.

Special precautions for storage
Epilim is hygroscopic. The tablets should not be removed from the container until immediately before they are taken. Store in a dry place below 30°C.

Nature and contents of container
Polypropylene tube with polyethylene cap. Pack size 30 tablets.

Manufactured by
Sanofi Winthrop Industrie
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