Epilim® 400mg Powder for injection/infusion
Sodium Valproate
Intravenous

Trade Name of the Medicinal Product
Epilim 400mg Powder for injection/infusion

Qualitative and Quantitative Composition

Freeze dried Powder	Per Vial
Sodium Valproate (DCI)	400mg
Solvent	Per Ampoule
Water for Injection	4ml

Pharmaceutical Form

Powder and Solvent for solution for injection/infusion.
The powder is hygroscopic, white or practically white crystalline.
The solvent is a clear, colourless solution.

CLINICAL PARTICULARS
Therapeutic Indications
The treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.
In the 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)

Posology and Method of Administration
Epilim Intravenous may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Epilepsy
Daily dosage requirements vary according to age and body weight.

To reconstitute, inject the solvent provided (4ml) into the vial, allow to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 100mg/ml.

Each vial of Epilim Intravenous is for single dose injection only. It should be reconstituted immediately prior to use and infusion solutions containing it used within 24 hours. Any unused portion should be discarded *(see Instructions for Use/Handling).*

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

Patients already satisfactorily treated with Epilim may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800mg depending on body weight (up to 10mg/kg) followed by continuous or repeated infusion up to a maximum of 2500mg/day.

Epilim Intravenous should be replaced by oral Epilim therapy as soon as practicable.

Use with children
Daily requirement for children is usually in the range 20-30mg/kg/day and method of administration is as above. Where adequate control is not achieved within this range the dose may be increased up to 40mg/kg/day but only in patients in

whom plasma valproic acid levels can be monitored. Above 40mg/kg/day clinical chemistry and Hematological parameters should be monitored.

Use in the 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 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 also 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 should be avoided as it can increase the risk of liver toxicity (*see Special Warnings*).

In female children, women of childbearing potential and pregnant women
Epilim 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 unless other treatments are ineffective or not tolerated.

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.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (See Pregnancy Prevention Program in Special Warnings and Precautions for Use).

Combined Therapy
When starting Epilim in patients already on other anticonvulsants, 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 anticonvulsants 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 Hematological 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*).

Contra-indications
Epilim is contraindicated in the following situations:

- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria
- Known urea cycle disorders
- Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see section Special warnings and special precautions for use *Patients at risk of hypocarnitinemia*).

- 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 Special warnings*).
- Treatment of epilepsy
  • in pregnancy unless there is no suitable alternative treatment (see Special Warnings and Precautions for Use and Pregnancy).
  • in women of childbearing potential, unless there is no other alternative treatment and unless the conditions of the pregnancy prevention program are fulfilled (see Special Warnings and Precautions for Use and Pregnancy)

Special Warnings and Precautions for Use

Special warnings
Liver dysfunction:

<u>Conditions of occurrence</u>:
Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, 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 Special warnings and special precautions for use) or degenerative disease.
After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years *(see aspirin/salicylate product information on Reye's syndrome).*

Monotherapy is recommended in children under the age of 3 years when prescribing 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

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

<u>Suggestive signs</u>:
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, malaise, anorexia, lethargy, edema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.
Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

<u>Detection</u>:
Liver function tests should be performed before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk (see also Interactions with other medication and other forms of interaction) and those with a prior history of liver disease.
Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.
Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of 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 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, 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 a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate (see section Contraindication and section Special warnings and special precautions for use, 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 with other medication and other forms of interaction, undesirable effects and overdose.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.
More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis: Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be discontinued.

Female children, women of childbearing potential and pregnant women (*see Pregnancy and Lactation*):

- **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 is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see Contraindication and pregnancy).
- in women of childbearing potential, unless there is no other alternative treatment and unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindication 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.
• 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 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 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.

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 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. These educational materials include a patient guide and patient card to be provided to all women of childbearing potential using valproate.
A risk acknowledgement form is intended 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 section 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. 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 should be provided to all men of reproductive potential using valproate.
Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during the time of conception, the Marketing Authorization Holder has provided educational materials to remind the warnings and provide guidance regarding use of valproate in men of reproductive potential, including a patient guide for male patients to be provided to all men of reproductive potential using valproate.

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 (see section Interactions with other medication and other forms of interaction).

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 risk is not known and the available data do not exclude the possibility of an increased risk for sodium valproate.

Therefore patients should be monitored for signs of suicidal ideation and 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.

Carbapenems agents
The concomitant use of Epilim and carbapenem agents is not recommended.

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 (see section Undesirable effects).

Precautions

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 *(see Undesirable Effects).*

Renal insufficiency
In patients with 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 *(see Posology and Method of Adminstration and Pharmacokinetic Properties).*

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 *(see Undesirable Effects).*

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.
Hyperammonaemia, which may be present in the absence of abnormal liver function tests, can occur in patients during treatment with sodium valproate. This may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, hyperammonaemic encephalopathy should be considered *(see Urea Cycle Disorders)* and Epilim should be discontinued.

Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients:
1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonaemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders.

Ornithine Transcarbamylase (OTC) Deficiency: The females who are heterozygous for OTC deficiency have a spectrum of clinical and biochemical findings, depending on the extent of inactivation of the X-chromosome. Females may show a range of symptoms due to hyperammonaemia which, may be episodic, and therefore difficult to diagnose. The acute symptoms include headaches, vomiting, irritability, bizarre behavior, lethargy, ataxia, tremors, seizures (generalised tonic-clonic or focal) and coma. Valproate may precipitate hyperammonaemia symptoms in those who have pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated symptomatic hyperammonaemia should be evaluated for OTC deficiency. Investigations should include measurement of plasma amino acids and the immediate cessation of valproate should result in clinical improvement

Weight gain: Epilim 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 Undesirable Effects)*.

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

Alcohol: Alcohol intake is not recommended during treatment with valproate.

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 Special Warnings and Precautions for Use and see also Interactions with Other Medicaments and Other Forms of Interaction).

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

Interactions with Other Medicaments and Other Forms of Interaction

Effects of valproate on other drugs

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

- ***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 combined therapy with dosage adjustment when appropriate.

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

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

- ***Lamotrigine***
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 %.

- ***Vitamin K-dependent anticoagulants***
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

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

Effects of other drugs on valproate
Antiepileptics
Antiepileptics 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 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 and chloroquine
Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Epilim may need adjustment.

Highly protein bound agents
In case of concomitant use of valproate and *highly protein bound agents (e.g. aspirin),* free valproic acid 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 antibiotics such as imipenem, panipenem and meropenem: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid levels within two days, sometimes associated with convulsions, Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilized on valproic acid should be avoided **(**see Special Warnings and Precautions for Use**).** If treatment with these antibiotics cannot be avoided, close monitoring of Epilim blood level should be performed.

Cholestyramine
Cholestyramine may decrease the absorption of valproate.

Rifampicin
Rifampicin may decrease the valproate 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, ritonavir decrease valproate plasma level 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 valproate serum 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 valproate serum levels as appropriate.

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

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

- ***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 Special Warnings and Precautions for Use "Severe liver damage" and "children").
Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see Special Warnings and Precautions for Use "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 Special Warnings and Precautions for Use).

- ***Topiramate and acetazolamide***

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at risk patients such as those with pre-existing 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 Special warnings and special precautions for use *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 Contra-indications and Special Warnings and Precautions for Use).

Teratogenicity and developmental effects from female and male exposure
Pregnancy Exposure Risk related to valproate
Valproate was shown to cross the placental barrier both in animal species and in humans (see section Pharmacokinetics).

In females, both valproate monotherapy and valproate polytherapy including other antiepileptics, 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 Special Warnings and Precautions for Use).

Congenital malformations from in utero exposure
A meta-analysis (including registries and cohort studies) showed that about 11% of children of epileptic women 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 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 to 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.

Neurodevelopment 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 untreated epileptic mothers.
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 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 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.

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 Special warnings and special precautions for use). 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.

Pregnant women
Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see section contraindication and Special warnings and special precautions for use).
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 an obstetrician 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 haemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia; and/or to 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 other anti-epileptic enzyme inducing drugs.
Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates, whose mothers have taken valproate during the third trimester of the pregnancy.

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 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 (see section Interactions with Other Medicaments and Other Forms of Interaction**)**.

Fertility
Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (*see Undesirable effects*). Valproate administration may also impair fertility in men (*see Undesirable effects*).
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

Lactation
Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of total maternal serum levels. Although there appears to be no contraindication to breastfeeding, physicians are advised that in any individual case, consideration should be given to the safety profile of Epilim, specifically Hematological disorders (*see Undesirable Effects*).

Effects on Ability to Drive and to Use Machines
Not applicable - use of intravenous formulation restricted to patients unable to take oral therapy. However, note use of Epilim may provide seizure control such that the patient may again be eligible to hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anticonvulsant polytherapy or association with benzodiazepines *(see Interactions with Other Medicaments and Other Forms of Interaction).*

Undesirable Effects
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 and Lactation).*

Hepato-biliary disorders
Common: liver injury, severe liver damage, including hepatic failure sometimes resulting in death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient.

Gastrointestinal disorders
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 the treatment.
*Also observed a few minutes after intravenous injection with spontaneous resolution within a few minutes.
Uncommon: pancreatitis, sometimes lethal (see section Special warnings and special precautions for use).

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) and it usually resolves spontaneously with parkinsonism, ataxia, paresthesia...

Uncommon: coma, encephalopathy, lethargy (see below), reversible parkinsonism, ataxia, paresthesia.

Uncommon: Aggravated convulsions (see Special Warnings and Precautions for Use).
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment and is usually transient. Cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbital or topiramate.. They have usually been reversible on withdrawal of treatment or reduction of dosage. An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioral deterioration have been reported.

Blood and lymphatic system disorders
Common: anemia, thrombocytopenia (see section Special warnings and special precautions for use).
Uncommon: pancytopenia, leucopenia. The blood picture returned to normal when the drug was discontinued.
Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anemia macrocytic, macrocytosis. Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.

Musculoskeletal and connective tissue disorders

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long term therapy with valproate. The mechanism by which valproate affect bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see section Special warnings and special precautions for use).

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 Special warnings and special precautions for use).

Rare: hyperammonaemia* (see section Special warnings and special precautions for use), obesity.
*Cases of isolated and moderate hyperammonemia without change in liver function tests may occur and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim should be discontinued. Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see Section Special warnings and special precautions for use. *Urea cycle disorders and risk of hyperammonemia* and *patients at risk of hypocarnitinemia*).
Not known: hypocarnitinemia (see Sections Contraindications and Special warnings and special precautions for use).

Vascular disorders
Common: hemorrhage (see section Special warnings and special precautions for use and section Pregnancy).
Uncommon: vasculitis.

General disorders and administration site conditions
Uncommon: hypothermia, non-severe edema peripheral.

Hepatobiliary disorders
Common: liver injury (see section Special warnings and special precautions for use and section Pregnancy).

Reproductive system and breast disorders
Common: dysmenorrhea.
Uncommon: amenorrhea.
Rare: male infertility, polycystic ovaries.
Very rarely gynaecomastia has occurred.

Psychiatric disorders
Common: confusional state, hallucinations, disturbance in attention*, aggression*, agitation*.
Rare: abnormal behavior*, psychomotor hyperactivity*, learning disorder*.
*These ADRs are principally observed in the pediatric population.

Skin and subcutaneous tissue disorders
Common: hypersensitivity, nail and nail bed disorders, transient and /or dose related alopecia. Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: angiedema, 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.

Eye disorders
Not known: diplopia.

Ear and labyrinth disorders
Common: deafness

Renal and urinary disorders
Common: urinary incontinence.
Uncommon: renal failure.
Rare: enuresis, tubuloinsterstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy but the mode of action is as yet unclear.

Respiratory, thoracic and mediastinal disorder

Uncommon: pleural effusion.

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 sections Special warnings and special precautions for use and Pregnancy), biotin deficiency/biotinidase deficiency.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: myelodysplastic syndrome.
Unknown: acquired Pelger–Huet anomaly

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 Special Warnings and Precautions for Use). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

Overdose
Cases of accidental and deliberate valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels *(see Pharmacokinetic Properties).* 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.
Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

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

Haemodialysis and hemoperfusion have been used successfully. Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. In case of massive overdose, haemodialysis and hemoperfusion have been used successfully.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Anti-epileptics; Fatty acid derivatives.
ATC code: N03AG01
Sodium valproate is an anticonvulsant.

In certain *in-vitro* studies it was reported that sodium valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication *ex-vivo* is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

Pharmacokinetic Properties
DISTRIBUTION *(see section Pregnancy)*

Placental transfer 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.

ELIMINATION
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 valproate serum levels (see Interactions with Other Medicaments and Other Forms of Interaction). 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.

The half-life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children. In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of 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.

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 untreated epileptic patients, provided contradictory results.
The biological significance of an increase in SCE frequency is not known.

CARCINOGENICITY

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 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 326. 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

List of Excipients
None.

Incompatibilities
Epilim Intravenous should not be administered via the same line as other IV additives.

Shelf Life
Do not use later than the date of expiry indicated on the outer packaging.

Special Precautions for Storage
Epilim freeze-dried powder should be stored below 30°C.
Reconstituted infusion solutions: at 2-8°C if stored before use, discarding any remaining solution after 24 hours.

Nature and Contents of Container
Colourless glass vial (Type I) with chlorobutyl rubber closure and crimped with an aluminium cap. The vial is supplied packed in a cardboard carton along with one ampoule containing 4ml of solvent (Water for Injection).

Instructions for Use/Handling
For intravenous use, the reconstituted solution should be used immediately and any unused portion discarded.

If the reconstituted solution is further diluted for use as an infusion solution, the dilute solution may be stored for up to 24 hours if kept at 2 to 8°C before use, discarding any remaining after 24 hours.

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