Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Epilim Chrono 300 Controlled Release

2. Qualitative and quantitative composition

Each tablet contains 199.8 mg Sodium Valproate and 87.0 mg Valproic Acid equivalent to 300 mg sodium valproate.

Excipient(s) with known effect:

Sodium 27.65 mg (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Prolonged Release Tablet

4. Clinical particulars

4.1 Therapeutic indications Female patients:

- For all female patients aged under 55 years: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all female patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

Male patients:

- For all male patients aged under 55 years initiating treatment with valproate: For the treatment of generalised, partial or other epilepsy only when there is no other effective or tolerated treatment.
- For all male patients established on treatment with valproate or male patients aged over 55 years: For the treatment of generalised, partial or other epilepsy.

4.2 Posology and method of administration Posology

Epilim Chrono is a prolonged release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day. Epilim Chrono may be given once or twice daily.

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 Epilim conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage

Usual requirements are as follows:

Adults

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

Special populations

Paediatric

population

Children over 20 kg: Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20 – 30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day. In children requiring doses higher than 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Children under 20 kg: An alternative formulation of Epilim should be used in this group of patients, due to the tablet size and need for dose titration. Epilim Liquid (sugar-free), Epilim Syrup or Epilim Chronosphere are alternatives.

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.

Renal impairment

It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

Hepatic impairment

Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see sections 4.4 and 4.8).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see sections 4.3 and 4.4).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition, in conjunction with valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see section 4.4.1).

Female children and women of childbearing potential aged under 55 years

No new female patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4 and 4.6).

Valproate must be supervised by a specialist experienced in the management of epilepsy.

Valproate should not be prescribed in female children and women of childbearing potential aged under 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3, 4.4

and 4.6).

Where possible, existing female children and women of childbearing potential aged under 55 years should be switched to another treatment unless two specialists independently consider and document there is no other effective or tolerated treatment. For those continuing to receive valproate, the benefits and risks of valproate should be carefully reconsidered at regular treatment reviews, at least annually (see section 4.4).

Valproate must be prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4).

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 (see section 4.6).

Male patients aged under 55 years

No new male children or men aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable (see sections 4.4 and 4.6).

The specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the risk of infertility in males (see sections 4.4, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

Combined therapy (see section 4.5)

When starting Epilim Chrono in patients already on other anti-convulsants, these should be tapered slowly; initiation of Epilim Chrono 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 – 10 mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, e.g. 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 Chrono. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

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 section 5.2).

Method of administration

Epilim Chrono Controlled Release Tablets are for oral administration. The tablets should be swallowed whole and not crushed or chewed.

In view of the sustained release process and the nature of the excipients in the formula, the inert matrix of the tablet is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released.

4.3 Contraindications

Epilim Chrono is contraindicated in the following situations:

- In pregnancy, unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.4 and 4.6).
- In women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Hypersensitivity to sodium valproate, valproic acid or any other excipients listed in section 6.1.
- Active liver disease, or personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria.
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the 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 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Special warnings

Liver dysfunction:

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4) or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see also section 4.5). Additionally, salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing valproate, but the potential benefit of valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see section

4.4Severe liver damage and also section 4.5).

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

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

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

Detection:

Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially for patients at risk and those with a prior history of liver disease. Upon changes in concomitant medicinal products (dose increase or additions) that are known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5).

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 valproate therapy.

As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.

As with most anti-epileptic 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.

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, valproate-induced acute liver failure and liver-related deaths have been reported 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 section 4.3).

Urea cycle disorders and risk of 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 (see sections 4.3 and 4.4).

Patients at risk of hypocarnitinaemia:

Valproate administration may trigger occurrence or worsening of hypocarnitinaemia 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 hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see section 4.4), 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 hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.

Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative. In these patients, carnitine monitoring 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 4.5, 4.8 and 4.9.

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 anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, valproate should be discontinued.

Female children, women of childbearing potential aged under 55 years and pregnant women:

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate

have a high risk for congenital malformations (11%) and neuro-developmental disorders (up to 30-40%) which may lead to permanent disability (see section 4.6).

Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Epilim Chrono is contraindicated in the following situations:

- In pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see sections 4.3 and 4.6).
- In women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The specialist must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to support her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient understands and acknowledges the risks of congenital malformations and neuro-developmental disorders which may lead to permanent disability, 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 4.6).
- 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 (for further details please refer to subsection contraception of this boxed 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 general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her GP for urgent referral to a specialist 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 apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The specialist must ensure that:

• The parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.

• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neuro-developmental disorders which may lead to

permanent disability including the magnitude of these risks for children exposed to valproate *in utero.* The specialist 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 other treatment options. If valproate is the only effective and tolerated treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to another treatment before they reach menarche.

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 support her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

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 and complete the Annual Risk Acknowledgement Form with the patient and/or carer at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider other treatment options. Every effort should be made to switch to an appropriate treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate 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 immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with valproate-exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:

- The Patient Card is provided with every valproate pack dispensation and that patients understand its content.
- Patients are advised not to stop valproate medication and to immediately contact their GP to be referred to a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy.

Male children and men

All male patients and/or carers should be made aware of the potential risk to children

born to men treated with valproate in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see sections 4.2, 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance (see section 5.3).

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients.
Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

For males aged under 55 years, at initiation of treatment, the specialist should discuss and complete the risk acknowledgement form with the patient and/or carer at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

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 (see section 4.8).

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data does not exclude the possibility of an increased risk for valproate.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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.

Excipient with known effect

Sodium: This medicinal product contains 27.65 mg sodium per tablet, equivalent to 1.38% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Precautions

Haematological 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 section 4.8).

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see sections 4.2 and 5.2).

Patient with systemic lupus erythematosus:

Although immune disorders have only rarely been noted during the use of valproate, the potential benefit of valproate should be weighed against its potential risk in patients with systemic lupus erythematosus (see section 4.8).

Weight gain:

Valproate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (see section 4.8).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Epilim on other drugs

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

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

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- ***Clozapine***

Concomitant treatment of valproate and clozapine may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of valproate with clozapine is necessary, careful monitoring for both events is required.

- ***Lithium***

Valproate has no effect on serum lithium levels.

- ***Olanzapine***

Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***

Valproate 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***

Valproate 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***

Valproate decreases phenytoin total plasma concentration. Moreover, valproate increases 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 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***

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

- ***Felbamate***

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

- ***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.

- ***Zidovudine***

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

- ***Nimodipine***

In patients concomitantly treated with valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

- ***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 Epilim

- ***Anti-epileptics***

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

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 hyperammonaemia.

On the other hand, combination of felbamate and valproate decreases valproic acid clearance by 22 – 50% and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.

- ***Anti-malarial agents***

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 valproate 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 plasma levels may be increased.

- ***Vitamin K-dependent factor 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.

- ***Cimetidine or erythromycin***

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

- ***Carbapenem antibiotics (such as 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 stabilised on valproic acid should

be avoided (see section 4.4). 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 level when co-administered.

- ***Cholestyramine***

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

- ***Oestrogen-containing products, including oestrogen-containing hormonal contraceptives***

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative 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) 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) and consider monitoring valproate serum levels as appropriate.

4.5.2 Other interactions

- ***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 4.4).

Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).

Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be

exercised when valproate is concomitantly used 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 4.4).

- ***Newer anti-epileptics (including topiramate and acetazolamide)***

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

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 (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

- ***Quetiapine***

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

4.6 Fertility, pregnancy and lactation

• Epilim is contraindicated in pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment (see section 4.3 and 4.4).

• Epilim is contraindicated for use in women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4

Teratogenicity and developmental effects

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 neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.

Valproate was shown to cross the placental barrier in both animal species and humans (see section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

Congenital malformations from in utero exposure

A meta-analysis (including registries and cohort studies) showed that approximately 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 (approximately 2 – 3%).

The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.

This risk is dose-dependent in valproate monotherapy, and available data suggests 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 and 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 or deafness 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 did not recover.

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

Neuro-developmental 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 neuro-developmental disorders which may lead to permanent disability (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 neuro-developmental disorders which may lead to permanent disability in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with 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 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 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 during pregnancy, although the role of confounding factors related to intellectual disability 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 population-based study 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 another population-based study 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 5.3).

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 humans do not allow for a conclusion on a potential dose-related effect.

Female children and woman of childbearing potential aged under 55 years

(see above and section 4.4) Oestrogen-containing products

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of
valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess 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 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate 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 sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred by her GP 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 the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose 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 (see section 4.2).

All patients with valproate-exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation 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

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic 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 hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1 – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from valproate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8).

Valproate administration may also impair fertility in men (see sections 4.2, 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). 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 group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, GPs and specialists should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their GP or specialist. For male patients planning to conceive a child, the specialist should consider and discuss other suitable treatment options with the male patients.
Individual circumstances should be evaluated in each case.

4.7 Effects on ability to drive and use machines

Use of Epilim Chrono may provide seizure control such that the patient may be eligible to

hold a driving licence.

Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines (see section 4.5).

4.8 Undesirable effects

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 the available data).

Congenital malformations and developmental disorders: (see sections 4.4 and 4.6).

Hepatobiliary disorders:

Common: liver injury (see section 4.4.1)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders

Very common: nausea

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim Chrono with or after food.

Uncommon: pancreatitis, sometimes lethal (see section 4.4)

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, 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 behavioural deterioration have been reported.

Psychiatric disorders:

Common: confusional state, hallucinations, aggression, agitation, disturbance in attention

Rare: abnormal behaviour, psychomotor hyperactivity, learning disorder

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Rare: hyperammonaemia* (see section 4.4.2), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur valproate should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see sections 4.3 and 4.4).

Not known: hypocarnitinaemia (see section 4.3 and 4.4).

Endocrine disorders:

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Rare: hypothyroidism (see section 4.6)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia, (see section 4.4.2)

Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis,

anaemia macrocytic, macrocytosis The blood picture returned to normal when

the drug was discontinued.

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 (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 (see section 4.6).

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.

Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

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

Not known: hyperpigmentation

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: polycystic ovaries, male infertility

(see section 4.6) Very rarely gynaecomastia

has occurred.

Vascular disorders:

Common: haemorrhage (see sections 4.4.2 and 4.6)

Uncommon: vasculitis

Eye disorders:

Rare: diplopia

Ear and labyrinth disorders:

Common: deafness, a cause-and-effect relationship has not been established.

Renal and urinary disorders:

Common: urinary incontinence

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe peripheral oedema

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 affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2)

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion (eosinophilic)

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 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic

syndrome *Unknown*: acquired

Pelger-Huet anomaly

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric 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 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the relevant National Regulatory Authority.

4.9 Over dose

Symptoms

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

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, 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 section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the Epilim formulations may lead to hypernatraemia when taken in overdose.

Management

Hospital management of overdose should be symptomatic, including cardio-respirato-gastric monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, Fatty acid derivatives, ATC code: N03A G01.

Mechanism of action

Sodium valproate and valproic acid are anti-convulsants.

The most likely mode of action for Epilim Chrono is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Clinical safety

In certain *in-vitro* studies it was reported that Epilim Chrono could stimulate HIV replication, but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Epilim Chrono does not have a mitogen-like effect on inducing HIV replication. Indeed, the effect of Epilim Chrono 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.

5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40 – 100 mg/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 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 Chrono may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see section 4.6)

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 foetuses, 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 Chrono is usually reported to be within the range of 8 – 20 hours.

Interaction with oestrogen-containing products

Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

Bioequivalence with other formulations

Epilim Chrono formulations are prolonged release formulations which demonstrate in

pharmacokinetic studies less fluctuation in plasma concentration compared with other established conventional and modified release Epilim formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of Epilim Chrono make the measurement of plasma levels less dependent upon time of sampling.

The Epilim Chrono formulations are bioequivalent to Epilim Liquid and gastro-resistant formulations with respect to the mean areas under the plasma concentration time curves. Steady-state pharmacokinetic data indicate that the peak concentration (C_{max}) and trough concentration (C_{min}) of Epilim Chrono lie within the effective therapeutic range of plasma levels found in pharmacokinetic studies with Epilim gastro-resistant tablets.

Special populations

Renal insufficiency

In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels (see section 4.2).

Paediatric population

Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric 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 and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 – 67 hours. In children aged 2 – 10 years, valproate clearance is 50% higher than in adults.

5.3 Preclinical safety data

Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.

Non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity

Valproate induced teratogenic effects (malformations of multiple organ systems) 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.

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

Testicular toxicity

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 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.

In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight was observed at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy was observed in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions were considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.

There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in animal studies and impaired fertility in adult patients (see section 4.6).

The toxicological significance of the testicular findings in juvenile animals has not been evaluated and hence the relevance to human testicular development, particularly in the paediatric population, is unknown.

Valproate is a known histone deacetylase (HDAC) inhibitor and has been reported to induce changes in epigenetic marks (histone acetylation, histone methylation, DNA methylation), changes in chromatin condensation and influence gene expression. The clinical relevance of these findings in relation to valproate's reproductive and developmental toxicity (see sections 4.6 and 5.3) is unknown.

6. Pharmaceutical particulars

6.1 List of excipients

Hypromellose

Ethylcellulose

Hydrated

Silica

Film Coat

Violet coat (Opadry 0Y-S-6705), containing:

Titanium dioxide (E171)

Erythrosine BS aluminium lake (E127)

Indigo carmine aluminium lake FD & C

Blue No. 2 (E132) Iron oxide black (E172)

Hypromellose (E464)

Macrogol 400

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Epilim Chrono is hygroscopic. The tablets should not be removed from their foil until immediately before they are taken. Where possible, blister strips should not be cut. Store in a dry place below 30°C.

6.5 Nature and contents of container

Epilim Chrono 300 Controlled Release tablets are supplied in blister packs further packed into a cardboard carton. Pack size 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Sanofi-aventis Kenya

8. Marketing authorization number(s)

H2008/19666/602/R1

9. Date of first authorisation/ renewal of the authorisation

26/09/2026

10. Date of revision of the text

13/08/2025