PRODUCT INFORMATION – VALPROATE-AFT (SODIUM VALPROATE) 100mg/mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Valproate-AFT Solution for Infusion or Injection is a sterile, non-pyrogenic solution:

- 300 mg/3 mL of solution packed in 5 mL capacity glass ampoule
- 400 mg/4 mL of solution packed in 5 mL capacity glass ampoule
- 1000 mg/10 mL of solution packed in 10 mL capacity glass ampoule

PHARMACEUTICAL FORM

Sodium Valproate 100 mg/mL, solution for infusion or injection, is a clear liquid and particles free in colourless glass ampoule.

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.

POSOLOGY AND METHOD OF ADMINISTRATION

Valproate-AFT s may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Dosage

Daily dosage requirements vary according to age and body weight. Each vial of Valproate-AFT is for single dose injection only. Valproate-AFT 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 Valproate-AFT 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 400-800 mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day. Valproate-AFT Intravenous should be replaced by oral sodium valproate therapy as soon as practicable.

<u>Use with children</u>

Daily requirement for children is usually in the range 20-30 mg/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 40 mg/kg/day but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day clinical chemistry and haematological parameters should be monitored.

<u>Use in the elderly</u>

Although the pharmacokinetics of Valproate-AFT 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.

<u>In patients with renal insufficiency</u>

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

In patients with hepatic insufficiency
Salicylates should not be used concomitantly with Valproate-AFT 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 Valproate-AFT, concomitant use in children under 3 years can increase the risk of liver toxicity (see Special Warnings).

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

Combined therapy
When starting Valproate-AFT in patients already on other anti-convulsants, these should be tapered slowly: initiation of Valproate-AFT 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 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 Valproate-AFT. 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 40 mg/kg/day clinical chemistry and haematological parameters should be monitored. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see *Pharmacokinetic Properties*).

CONTRAINDICATIONS
Valproate-AFT is contraindicated in the following situations:

- In epilepsy
  - valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
  - valproate is contraindicated in women of childbearing potential, unless the conditions to prevent pregnancy are fulfilled (see Female children, Women of childbearing potential, pregnant women section)
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders
- Hypersensitivity to sodium valproate
- Porphyria
- Valproate is contraindicated in 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 Special warnings and precautions for use).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 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 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 Valproate-AFT, but the potential benefit of Valproate-AFT 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.

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 in those who seem most at risk, 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 Valproate-AFT 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.

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

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 counselling 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.

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-AFT should be discontinued.

Female children, Women of childbearing potential, pregnant women
Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Valproate-AFT is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In women of childbearing potential unless below conditions are fulfilled.

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee 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 has understood and acknowledged 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 (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 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 acknowledged that she has understood the hazards and necessary precautions associated with valproate use.

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.

Female children
The prescriber must ensure that:

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

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

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

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section interaction). 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. Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient.

Pregnancyplanning
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. 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 be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

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

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 do not exclude the possibility of an increased risk for sodium valproate.

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

Carbapenemagents
The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, 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, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see *Contraindication*).

PRECAUTIONS

Haematological: 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 dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see *Dosage and Method of Administration and Pharmacokinetic Properties).*

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Valproate-AFT, the potential benefit of Valproate-AFT 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-AFT.

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 sodium valproate should be discontinued.

Urea cycle disorders: 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 Contraindication) 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 Xchromosome. Females may show a range of symptoms due to hyperammonemia 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 hyperammonemia symptoms in those who have pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated symptomatic hyperammonemia 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: Valproate-AFT 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 Undesirable Effects*).

Diabetic patients: Valproate-AFT 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.

Carnitine palmitoyltransferase (CPT) type II deficiency: Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Valproate-AFT.

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of Valproate-AFT on other drugs
Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Valproate-AFT 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.

Lithium
Valproate-AFT has no effect on serum lithium levels.

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

Phenobarbital

Valproate-AFT 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-AFT 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-AFT decreases phenytoin total plasma concentration. Moreover Valproate-AFT 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-AFT was administered with carbamazepine as Valproate-AFT may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine
Valproate-AFT 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-AFT may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Nimodipine
In patients concomitantly treated with sodium 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-AFT may cause a small decrease in the clearance

of temozolomide that is not thought to be clinically relevant.

Vitamin K-dependent factor anticoagulants
The anti-coagulant 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.

Effects of other drugs on Valproate-AFT

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-AFT decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Valproate-AFT 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-AFT may need adjustment.

Highly protein bound agents
In case of concomitant use of Valproate-AFT and ***highly protein bound agents (e.g. aspirin)***, free valproic acid plasma levels may be increased.

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 *Special Warnings and Precautions For Use*). 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. 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.

Other Interactions
Caution is advised when using Valproate-AFT 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.

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

FERTILITY, PREGNANCY AND LACTATION

Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.

Valproate is contraindicated for use in women of childbearing potential unless the above-mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section).

Teratogenicity and developmental effects
Pregnancy Exposure Risk related to valproate
Both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that anti- epileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

Valproate was shown to cross the placental barrier both in animal species and in humans (see section Pharmacokinetic properties). In animals teratogenic effects have been demonstrated in mice, rats and rabbits (See Preclinical safety data).

Congenital malformations
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.

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a

threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor 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 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 did not recover. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental disorders
Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed *in utero* to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes.

Available data from a 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.

Female children and woman of childbearing potential (see above and Special Warnings and Precautions For Use).

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.

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. 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. 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 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.

All patients with valproate-exposed pregnancy and their partners should be referred 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 common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

<u>Risk in the neonate</u>
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.

<u>Breast-feeding</u>
Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Valproate-AFT 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 *Undesirable effects*). Valproate administration may also impair fertility in men (see *Undesirable effects*). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable - use of intravenous formulation restricted to patients unable to take oral therapy.

However, note use of Valproate-AFT 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 anti- convulsant polytherapy or association with benzodiazepines (see *Interactions with Other Medicinal Products and Other Forms of Interaction*).

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 available data).

Congenital malformations and developmental disorders (see Special Warnings and Precautions For Use and Fertility, Pregnancy and Lactation).

Hepato-biliary disorders

Common: liver injury (see Special warnings). Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see Posology and Method of Administration, Contraindication and Warnings). Increased liver enzymes are common, particularly early in treatment, and may be transient (see Special warnings).

Gastrointestinal disorders
Very common: nausea, occurs a few minutes after intravenous injection with spontaneous resolution within a few minutes

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.

Uncommon: pancreatitis, sometimes lethal, (see *Special Warnings and Precautions for Use*).

Nervous system disorders
Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, dizziness may occur within a few minutes and it usually resolves spontaneously within a few minutes

Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia. aggravated convulsions

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*

*These ADRs are principally observed in the paediatric population.

Metabolic and nutrition disorders
Common: hyponatraemia, weight increased*

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

Rare: hyperammonaemia* (see *Precautions*), 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-AFT should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported (see Precautions). In such cases further investigations should be considered.

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

Rare: hypothyroidism (see *Fertility, pregnancy and lactation)*

Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia, (see *Precautions*). Uncommon: pancytopenia, leucopenia. The blood picture returned to normal when the drug was discontinued.

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia 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 (Valproate-AFT 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 also *Fertility, Pregnancy and Lactation*).

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.

Reproductive system and breast disorders
Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries Very rarely gynaecomastia has occurred.

Vascular disorders
Common: haemorrhage (see *Precautions; Fertility, pregnancy and lactation*). 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-AFT therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema. When using Valproate-AFT intravenously, nausea or dizziness may occur a few minutes after injection; they disappear spontaneously within a few minutes.

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

Rare: systemic lupus erythematosus, rhabdomyolysis (see *Precautions*)

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).

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

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. 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-AFT overdose 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. Signs of acute 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 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 *Pharmacokinetic Properties*).

Cases of intracranial hypertension related to cerebral oedema have been reported. The presence of sodium content in the Valproate-AFT formulations may lead to hypernatraemia 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. Haemodialysis and haemoperfusion 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 haemoperfusion have been used successfully.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics; Fatty acid derivatives, ATC code: N03AG01

Sodium valproate is an anti-convulsant. 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

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 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 sodium valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see **section Fertility, pregnancy and lactation**)

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

In animal species, valproate crosses the placenta to a similar extent as in humans.

In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism

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

Elimination

The half-life of 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.

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.

Preclinical 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. 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 1250 mg/kg/day and 150 mg/kg/day, respectively.

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
Monobasic potassium phosphate, Disodium phosphate dodecahydrate and Water for injections.

Incompatibilities
Valproate-AFT should not be administered via the same line as other IV additives.

Shelf life
48 months

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions

Special precautions for storage
Store below 30°C.

Nature and contents of container
Valproate-AFT Solution for infusion or injection is packed in type I transparent glass ampoules of 5 mL and 10 mL.

Special precautions for disposal
Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Presentation
3 mL of solution packed in a 5 mL capacity glass ampoule.
4 mL of solution packed in a 5 mL capacity glass ampoule.
10 mL of solution packed in a 10 mL capacity glass ampoule.
Available in packs of 1, 4, and 5 ampoules.

Manufacturer
Labiana Pharmaceuticals
C/ Casanova, 27-31,
08757 – Corbera de Llobregat
Barcelona, Spain

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