PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

AGUETTANT Sodium Valproate 400 mg/4 ml, Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AGUETTANT Sodium Valproate 400 mg/4 ml Solution for Injection or Infusion is a clear colourless sterile solution containing sodium valproate 400 mg in 4 mL water for injections in an ampoule.

The pH of the solution ranges from 7.0 to 9.0.

Excipient with known effect: Sodium.

This medicinal product contains 55.32 mg sodium per 4 mL ampoule, equivalent to 2.77 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for Injection or Infusion.

A clear colourless solution.

4. CLINICAL PARTICULARS

4.1. 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.

4.2. Posology and method of administration

Route of administration: intravenous injection or infusion.

AGUETTANT Sodium Valproate may be given by direct slow intravenous injection or by infusion using a separate intravenous line in sodium chloride 0.9% (normal saline), dextrose 5% or dextrose 5% in sodium chloride 0.9% (dextrose saline).

Daily dosage requirements vary according to age and body weight.

Each ampoule of AGUETTANT Sodium Valproate is for single dose injection only. Any unused portion should be discarded (see section *6.6 Special precautions for disposal and other handling*).

AGUETTANT Sodium Valproate 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 sodium valproate may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3-5 minutes, usually 400-800mg depending on body weight (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2500 mg/day. AGUETTANT Sodium Valproate should be replaced by oral therapy as soon as practicable.

Use with children

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.

Use in the elderly

Although the pharmacokinetics of AGUETTANT Sodium Valproate are modified in the elderly, they have

limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased.

This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency

It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section *5.2 Pharmacokinetic Properties*).

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with AGUETTANT Sodium Valproate since they employ the same metabolic pathway (see section *4.4 Special warnings and precautions for use* and section *4.8 Undesirable effects*).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see section *4.3 Contraindications* and section *4.4 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 AGUETTANT Sodium Valproate, concomitant use in children under 3 years can increase the risk of liver toxicity (see section *4.4 Special warnings and precautions for use*).

Female children and women of childbearing potential

Sodium valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see section *4.3 Contraindications,* section *4.4 Special warnings and precautions for use* and section *4.6 Fertility, pregnancy and lactation*).

Sodium valproate is prescribed and dispensed according to the sodium valproate Pregnancy Prevention Programme. The benefit and risk should be carefully reconsidered at regular treatment reviews (see section *4.4 Special warnings and precautions for use*).

AGUETTANT Sodium Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Combined Therapy

When starting AGUETTANT Sodium Valproate in patients already on other anti-convulsants, these should be tapered slowly: initiation of AGUETTANT Sodium Valproate therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anti-convulsants which induce liver enzyme activity, 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 AGUETTANT Sodium Valproate. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

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

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section *5.2 Pharmacokinetic properties*).

4.3. Contraindications

AGUETTANT Sodium Valproate is contraindicated in the following situations:

In epilepsy

- sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.

- sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see section *4.4 Special warnings and precautions for use* and section *4.6 Fertility, pregnancy and lactation*).

In bipolar disorder

- sodium valproate is contraindicated in pregnancy (see section *4.4 Special warnings and precautions for use* and section *4.6 Fertility, pregnancy and lactation*).
- sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see *Female children, Women of childbearing potential, and pregnant women* section).

All indications

- Hypersensitivity to sodium valproate
- Acute or chronic hepatitis
- Patient or family history of severe hepatitis, especially drug related
- Hepatic porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG, e.g. Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having a POLG-related disorder (see section *4.4 Special warnings and precautions for use*)
- Patients with known urea cycle disorders (see section 4*.4 Special warnings and precautions for use*)
- Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see section *4.4 Special warnings and precautions for use - Patients at risk of hypocarnitinemia*).

4.4. Special warnings and precautions for use

Special warnings

Female children, Women of childbearing potential, and pregnant women:

Sodium valproate has a high teratogenic potential and children exposed *in utero* to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section *4.6 Fertility, pregnancy and lactation*).

Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication (see section *4.3 Contraindications* and section *4.6 Fertility, pregnancy and lactation*).
- In pregnancy for bipolar disorder indication (See section *4.3 Contraindications* and section *4.6 Fertility, pregnancy and lactation*).
- In women of childbearing potential unless below conditions are fulfilled (see section *4.3 Contraindications* and section *4.6 Fertility, pregnancy and lactation*).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion 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 sodium valproate in utero.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section *4.6 Fertility, pregnancy and lactation*).

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

- 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 sodium valproate.
- The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The prescribers must ensure that:

- The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium 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 sodium valproate *in utero*.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium 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 prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

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

Annual treatment reviews by a prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning
If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium 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 *4.6 Fertility, pregnancy and lactation*). If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy
If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with a sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section *4.6 Fertility, pregnancy and lactation*).

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

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

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber, at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

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

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 sodium valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see section *4.6 Fertility, pregnancy and lactation*).

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 sodium valproate and for 3 months after stopping the treatment. The risk to children born to men stopping sodium valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without sodium valproate exposure) is not known.

The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used sodium 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 sodium valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with sodium valproate use (Annual Risk Acknowledgement Form).

Educational materials are available for healthcare professionals and male patients. A patient guide and a patient card should be provided to all men of reproductive potential using sodium valproate.

Severe liver damage

Conditions of occurrence:

Severe liver damage resulting sometimes in fatalities, has exceptionally been reported. Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see section *4.4 Special warnings and precautions for use*) or degenerative disease.

After the age of 3 years, the risk is significantly reduced, and it progressively decreases with age.

In most cases, such liver damage occurred during the first 6 months of therapy.

Suggestive signs:

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

- non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

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

Detection:

Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy, especially in patients at risk (see also section *4.5 Interactions with other medicinal products and other forms of interaction*). Among the usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of AGUETTANT Sodium Valproate therapy. As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they follow the same metabolic pathway.

Patients with known or suspected mitochondrial disease:

Sodium valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with sodium valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section *4.3 Contraindications*).

Urea cycle disorders and risk of hyperammonemia:

When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with AGUETTANT Sodium Valproate (see section 4.3 Contraindications and section *4.4 Special warnings and precautions for use*- Patients at risk of hypocarnitinemia and Severe liver damage).

Patients at risk of hypocarnitinemia

Sodium valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Sodium valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with sodium valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see section *4.4 Special warnings and precautions for use* - Warnings on Patients with known or suspected mitochondrial disease and urea cycle disorders and risk of hyperammonemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

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

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

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

See also section *4.5 Interactions with other medicinal products and other forms of interaction, section 4.8 Undesirable effects* and section *4.9 Overdose*.

PANCREATITIS:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING SODIUM VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HAEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, SODIUM VALPROATE SHOULD BE DISCONTINUED.

Suicidal ideation and behavior:

Potential for an increase in risk of suicidal thoughts or behaviors.

Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of anti- epileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this effect is not known.

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

Severe Cutaneous Adverse Reactions and Angioedema

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with sodium 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 sodium valproate and carbapenem agents is not recommended (See section 4.5 *Interactions with other medicinal products and other forms of interaction*).

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 sodium valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.

Estrogen-containing products

Sodium valproate does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of sodium valproate, which may result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of serum sodium valproate levels (see section *4.5 Interactions with other medicinal products and other forms of interaction*).

Liver function tests

Liver function tests should be carried out before therapy (see section *4.3 Contraindications*), and periodically during the first 6 months especially in patients at risk (see section *4.4 Special warnings and precautions for use* and see also section *4.5 Interactions with other medicinal products and other forms of interaction*). As with most antiepileptic drugs, a slight increase in liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Hematological tests:

Blood tests (blood cell count, including platelet count, bleeding time) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section *4.8 Undesirable effects*).

Patients with systemic lupus erythematosus:

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

Weight gain:

Very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize the risk (see section *4.8 Undesirable effects*).

Alcohol:

Alcohol intake is not recommended during treatment with sodium valproate.

Children

Monotherapy is recommended in children under the age of 3 years when prescribing AGUETTANT Sodium Valproate, but the potential benefit of AGUETTANT Sodium Valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see section *4.4 Special warnings and precautions for use* and see also section *4.5 Interactions with other medicinal products 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.

Renal insufficiency:

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

4.5. Interactions with other medicinal products and other forms of interaction

Effects of sodium valproate on other drugs

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

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

- ***Lithium***

AGUETTANT Sodium Valproate has no effect on serum lithium levels.

- ***Phenobarbital***

AGUETTANT Sodium 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***

AGUETTANT Sodium 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 a combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

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

- ***Carbamazepine***

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

- ***Lamotrigine***

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

- ***Zidovudine***

Sodium valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- ***Felbamate***

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

- ***Olanzapine***

Valproic acid may decrease the olanzapine plasma concentration.

- ***Rufinamide***

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

- ***Propofol***

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

- ***Nimodipine***

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

Effects of other drugs on sodium valproate

- ***Anti-epileptics***

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

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

Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia.

- ***Mefloquine***

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.

- ***Highly protein bound agents***

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

- ***Vitamin K-dependent factor anti-coagulant***

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

- ***Cimetidine or erythromycin***

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

- ***Carbapenem agents:***

Carbapenem (panipenem, imipenem and meropenem…): Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co- administration of carbapenem agents in patients stabilized on valproic acid should be avoided (see section *4.4 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, sodium valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors***

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

- ***Cholestyramine***

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

- ***Estrogen-containing products***

Estrogen-containing products, including estrogen-containing hormonal contraceptives may increase the clearance of sodium valproate, which may result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control), when adding, or discontinuing estrogen- containing products. Consider monitoring of sodium valproate plasma levels.

Sodium valproate usually has no enzyme inducing effect; as a consequence, sodium valproate does not reduce efficacy of estroprogestative agents in women receiving hormonal contraception.

- ***Metamizole***

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

- ***Methotrexate***

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

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 Special warnings and precautions for use*- “Severe liver damage” and “children”).

Concomitant use of sodium valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section *4.4 Special warnings and precautions for use*- “Severe liver damage” and “children”).

In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and sodium valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Appropriate liver monitoring should be exercised when sodium valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section *4.4 Special warnings and precautions for use*).

Topiramate and acetazolamide

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

Pivalate-conjugated medicines

Concomitant administration of sodium valproate and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see section *4.4 Special warnings and precautions for use - Patients at risk of hypocarnitinemia*). Concomitant administration of these medicines with sodium valproate is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

Quetiapine

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

4.6. Fertility, pregnancy and lactation

Pregnancy

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Sodium valproate is contraindicated for use in women of childbearing potential unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see section *4.5 Contraindications* and section *4.4 Special warnings and precautions for use*)

Pregnancy Exposure Risk related to sodium valproate

Both sodium valproate monotherapy and sodium valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a greater risk of congenital malformations than sodium valproate monotherapy.

Teratogenicity and developmental effects from female and male exposure

Sodium valproate was shown to cross the placental barrier both in animal species and in humans (see section *5.2 Pharmacokinetic properties*).

Pregnancy Exposure Risk related to sodium valproate

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

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3 Preclinical safety data - *Carcinogenicity*).

Risk to children of fathers treated with sodium 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 sodium 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 sodium 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 sodium valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see section *4.4 Special warnings and precautions for use*).

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to sodium 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.

Developmental disorders

Data have shown that exposure to sodium 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 sodium 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 sodium valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to sodium valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to sodium valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to sodium valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see sections *4.3 Contraindications* and *4.4 Special warnings and precautions for use*).

If a Woman plans a Pregnancy

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium 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 sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor 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 sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:

- Use the lowest effective dose and divide the daily dose sodium 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 to avoid high peak plasma concentrations.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor 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 sodium valproate exposure.

<u>Risk in the neonate</u>

- Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors, afibrinogenemia has also been reported and may be fatal. However, this syndrome must be

distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers.

- Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycemia have been reported in neonates whose mothers have taken sodium valproate during the third trimester of the pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken sodium valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken sodium valproate during the last trimester of the pregnancy.

Estrogen-containing products

Sodium valproate does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of sodium valproate, which may result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of serum sodium valproate levels (see section *4.5 Interactions with other medicinal products and other forms of interaction*).

Lactation

Excretion of sodium valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels. Based on literature and clinical experience, breastfeeding can be envisaged, taking into account AGUETTANT Sodium Valproate safety profile, especially hematological disorders (see section *4.8 Undesirable effects*).

Fertility

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using sodium valproate (see section *4.8 Undesirable effects*). Sodium valproate administration may also impair fertility in men (see section *4.8 Undesirable effects*). In the few cases in which sodium valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

4.7. Effects on ability to drive and use machines, or performing other hazardous tasks

Patients, notably drivers and machine operators, should be warned of the risk of drowsiness, especially in cases of anticonvulsant polytherapy or combination with other medicinal products that may increase drowsiness.

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, familial and genetic disorders: (see section *4.6 Fertility, pregnancy and lactation*)

Blood and lymphatic system disorders:

Common: anemia, thrombocytopenia, (see section *4.4 Special warnings and precautions for use*). Uncommon: pancytopenia, leucopenia

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

Investigations:

Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged (See section *4.4 Special warnings and precautions for use* and section *4.6 Fertility, pregnancy and lactation*), biotin deficiency/biotinidase deficiency.

Nervous system disorders:

Very common: tremor

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

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

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

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

Eye disorders:

Not known: diplopia.

Ear and labyrinth disorders:

Common: Deafness.

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion.

Gastrointestinal disorders

Very common: nausea*

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing treatment.

*Also observed a few minutes after intravenous injection with spontaneous resolution within a few minutes.

Uncommon: pancreatitis, sometimes lethal, (see section *4.4 Special warnings and precautions for use*).

Renal and urinary disorders:

Common: urinary incontinence.

Uncommon: renal failure.

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

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, transient and or dose related alopecia, nail and nail bed disorders. Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair color changes, hair growth abnormal)

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

Not known: hyperpigmentation

Musculoskeletal and connective tissue disorders:

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

Rare: systemic lupus erythematosus, rhabdomyolysis (see section *4.4 Special warnings and precautions for use*).

Endocrine Disorders:

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

Rare: hypothyroidism (see section *4.6 Fertility, pregnancy and lactation*).

Metabolism and nutrition disorders:

Common: hyponatremia, weight increased*

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

Rare: hyperammonemia* (see section *4.4 Special warnings and precautions for use*), obesity

*Cases of isolated and moderate hyperammonemia without change in liver function tests may occur and should not cause treatment discontinuation.

Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see section *4.4 Special warnings and precautions for use*- Urea cycle disorders and risk of hyperammonemia and patients at risk of hypocarnitinemia).

Not known: hypocarnitinemia (see section *4.3 Contraindications and* section *4.4 Special warnings and precautions for use*).

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

Rare: myelodysplastic syndrome.

Not known: acquired Pelger–Huet anomaly.

Vascular disorders:

Common: hemorrhage (see section *4.4 Special warnings and precautions for use* and section *4.6 Fertility, pregnancy and lactation*).

Uncommon: vasculitis.

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe oedema peripheral.

Hepatobiliary disorders:

Common: liver injury (see section *4.4 Special warnings and precautions for use).*

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Psychiatric disorders:

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

Rare: abnormal behavior*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the pediatric population.

Pediatric population

The safety profile of sodium valproate in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section *4.4 Special warnings and precautions for use*). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

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.

4.9. Overdose

Signs and Symptoms

Signs of acute massive overdose, usually include a coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock. Deaths have occurred following massive overdose nevertheless, a favorable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral edema have been reported.

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

Management

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

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

Naloxone has been successfully used in a few isolated cases.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTI-EPILEPTIC, ATC code: N03AG01.

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

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

5.2. Pharmacokinetic properties

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

Distribution
The percentage of free (unbound) drug is usually between 6-15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The pharmacological (or therapeutic) effects of AGUETTANT Sodium Valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see section *4.6 Fertility, pregnancy and lactation*).

Sodium valproate crosses the placental barrier in animal species and in humans:

- In animal species, sodium valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of sodium valproate in the umbilical cord of neonates at delivery. Sodium 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 sodium valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

Elimination
The half-life of AGUETTANT Sodium Valproate is usually reported to be within the range 8 – 20 hours. Based on limited data from literature, an approximate 20% increase in sodium valproate clearance has been reported in some patients that were concomitantly treated with sodium valproate and estrogen-containing products, which may result in a decrease in serum sodium valproate levels (see section *4.5 Interactions with other medicinal products and other forms of interaction*). Inter-individual variability has been noted. There are insufficient data to establish a robust PK- PD relationship resulting from this PK interaction.
Based on published literature, in pediatric patients below the age of 10 years, the systemic clearance of sodium valproate varies with age. In neonates and infants up to 2 months of age, sodium valproate clearance is decreased when compared to adults. In children aged 2-10 years, sodium valproate clearance is 50% higher than in adults. Above the age of 10 years, children and adolescents have sodium valproate clearances similar to those reported in adults.

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

5.3. Preclinical safety data

Genotoxicity

Sodium 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, sodium valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice.

In literature, after intraperitoneal exposure to sodium 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 sodium valproate as compared to healthy subjects not exposed to sodium valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with sodium valproate versus patients with untreated epilepsy, provided contradictory results. The biological significance of an increase in SCE frequency is not known.

Carcinogenocity

The 2-year carcinogenicity studies were conducted in mice and rats given oral sodium 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 sodium valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

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

In a fertility study in rats, sodium 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injections.

6.2. Incompatibilities

AGUETTANT Sodium Valproate should not be administered via the same line as other additives (see section 4.*2 Posology and method of administration*).

6.3. Shelf life

3 years

6.4. Storage Conditions

Store below 30°C.

For direct i.v. injection use: the solution should be used immediately, and any unused portion discarded.

For infusion use: the diluted solution may be stored for up to 24 hours if kept at 2 - 8°C before use, discarding any remaining after 24 hours.

6.5. Nature and content of container

4 ml of AGUETTANT Sodium Valproate solution is filled into 5 ml colourless, clear type I glass ampoules with a One Point Cut (OPC) break-system; box of 10 ampoules.

6.6. Special precautions for disposal and other handling

Instructions for dilution

Each ampoule of AGUETTANT Sodium Valproate is for single dose injection only.

For direct i.v. injection use: the solution should be used immediately, and any unused portion discarded.

For infusion use: the diluted solution may be stored for up to 24 hours if kept at 2 - 8°C before use, discarding any remaining after 24 hours.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MANUFACTURER/ PRODUCT REGISTRATION HOLDER

Manufacturer:

LABORATOIRE AGUETTANT
1 Rue Alexander Fleming
Lyon, 69007
France

Product Registration Holder:

FIRST PHARMACEUTICAL SDN BHD
20, Jalan SS 19/5
47500 Subang Jaya
Selangor
Malaysia

8. DATE OF REVISION OF PI

March 2025