1 NAME OF THE MEDICINAL PRODUCT

Sodium Valproate Advagen Solution for Injection or Infusion 100mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 100 mg sodium valproate.

Each 3 ml vial contains 300 mg sodium valproate.
Each 4 ml vial contains 400 mg sodium valproate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

A clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of patients with epilepsy who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.

In the treatment of generalized or partial epilepsy, particularly with the following patterns of seizures:

− absence

− myoclonic

− tonic-clonic

− atonic

− mixed

As well as, for partial epilepsy:

− simple or complex seizures

− secondary generalized seizures

− specific syndromes (West, Lennox-Gastaut)

4.2 Posology and method of administration

Posology

Dosage

Daily dosage requirements vary according to age and body weight.

Each vial of Sodium valproate injection is for single dose injection only.

Adults

Patients already satisfactorily treated with oral 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 – 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.

Sodium valproate injection should be replaced by oral sodium valproate therapy as soon as practicable.

Special populations

Paediatric population

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

Elderly

Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Renal impairment

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

Hepatic impairment

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

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

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

Female children and women of childbearing potential

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 sections 4.3, 4.4 and 4.6).

In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, 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 during pregnancy.

Combined therapy (see section 4.5)

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

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

Method of administration

Sodium valproate injection may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5%, or dextrose saline.

Sodium valproate injection should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion by polyethylene or glass containers.

4.3 Contraindications

Sodium Valproate Advagen Solution for Injection or Infusion 100mg/ml is contraindicated in the following situations:

- In pregnancy, unless there is no suitable alternative treatment (see sections 4.4 and 4.6).
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Hypersensitivity to sodium valproate or any other excipients listed in section 6.1.
- Active liver disease, or personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders (see section 4.4).
- Porphyria.
- Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia

- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms

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

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

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 therapy.
As a matter of precaution and in case they are taken concomitantly salicylates should also be discontinued since they employ the same metabolic pathway.
As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Patients at risk of hypocarnitinemia

Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also 4.4.1 Warnings on Patients with known or suspected mitochondrial disease and 4.4.2 urea cycle disorders and risk of hyperammonemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.

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

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

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

See also Sections 4.5 Interactions with other medication and other forms of interaction, 4.8 undesirable effects and 4.9 overdose.

As with most antiepileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:

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

Female children, women of childbearing potential and pregnant women:

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neuro-developmental disorders (see section 4.6).

Sodium Valproate Advagen Solution for Injection or Infusion 100mg/ml is contraindicated in the following situations:

- In pregnancy, unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

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 neuro-developmental 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 received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

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

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 neuro-developmental 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 programme 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 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist
The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss 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 specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy
If a woman using valproate becomes pregnant, she must 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 (see section 4.6).

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.

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

Aggravated convulsions:

As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:

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

available data does not exclude the possibility of an increased risk for sodium valproate.

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

Carbapenem agents:

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, 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).

4.4.2 Precautions

Haematological tests:

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

Renal insufficiency:

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

Patients with systemic lupus erythematosus:

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

Hyperammonaemia:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

Hyperammonaemia, which may be present in the absence of abnormal liver function tests, can occur in patients during treatment with sodium valproate. This may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, hyperammonaemic encephalopathy should be considered (see Urea Cycle Disorders) and valproate should be discontinued.

Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients:

1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonaemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders.

Ornithine Transcarbamylase (OTC) Deficiency:

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

Urea cycle disorders:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate (see section 4.3).

Weight gain:

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

Diabetic patients:

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

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.

Alcohol:

Alcohol intake is not recommended during treatment with valproate.

Sodium:

This medicinal product contains 28 mg sodium per ml, equivalent to 1.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of sodium valproate injection on other drugs

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

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

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

- ***Lithium***

  Valproate has no effect on serum lithium levels.

- ***Olanzapine***

  Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***

  Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

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

- ***Carbamazepine***

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

- ***Lamotrigine***

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

- ***Felbamate***

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

- ***Rufinamide***

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

- ***Propofol***

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

- ***Zidovudine***

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

- ***Nimodipine***

In patients concomitantly treated with 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 may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

4.5.2 Effects of other drugs on Sodium valproate injections

- ***Anti-epileptics***

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

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

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

- ***Anti-malarial agents***

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

- ***Highly protein bound agents***

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

- ***Vitamin K-dependent factor anticoagulants***

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

- ***Cimetidine or erythromycin***

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

- ***Carbapenem antibiotics (such as panipenem, imipenem and meropenem)***

  Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60 – 100% decrease in valproic acid levels within two days, sometimes associated with convulsions.

Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

- ***Rifampicin***

  Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

- ***Protease inhibitors***

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

- ***Cholestyramine***

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

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

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

  On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

- ***Metamizole***

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

- ***Methotrexate***

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

4.5.3 Other interactions

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

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

Concomitant administration of valproate and ***topiramate*** or ***acetazolamide*** has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- ***Quetiapine***

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

4.6 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 conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and developmental effects

Pregnancy exposure risk related to valproate

Both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data shown an increased risk of major congenital malformations and neuro-developmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.

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

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

Congenital malformations

A meta-analysis (including registries and cohort studies) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2 – 3%).

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

This risk is dose-dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or 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.

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

Neuro-developmental disorders

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

The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

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

Intelligence quotient (IQ) measured in children (age 6) with a history of valproate exposure *in utero* was on average 7 – 10 points lower than those children exposed to other anti-epileptics. 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 section 4.4)

Oestrogen-containing products

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in

decreased serum concentration of valproate and potentially decreased valproate efficacy (see sections 4.4 and 4.5).

If a woman plans a pregnancy

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

<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.

Breast-feeding

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

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

Fertility

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

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

4.7 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 Sodium valproate injection may provide seizure control such that the patient may again be eligible to hold a driving licence.

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

4.8 Undesirable effects

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

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

Hepatobiliary disorders:

Common: liver injury (see section 4.4.1)

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

Gastrointestinal disorders:

Very common: nausea, 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. These problems can usually be overcome by taking Sodium valproate injection with or after food.

Uncommon: pancreatitis, sometimes lethal (see section 4.4)

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, 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 (see section 4.4)

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

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

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:

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

Rare: abnormal behaviour, psychomotor hyperactivity, learning disorder

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 4.4).

Rare: hyperammonaemia* (see section 4.4.2), obesity

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

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2). 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 section 4.6)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia (see section 4.4.2)

Uncommon: pancytopenia, leucopenia

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

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see also section 4.6).

Skin and subcutaneous tissue disorders:

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

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

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

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: polycystic ovaries, male infertility (see section 4.6)

Very rarely gynaecomastia has occurred.

Vascular disorders:

Common: haemorrhage (see sections 4.4.2 and 4.6)

Uncommon: vasculitis

Eye disorders:

Rare: diplopia

Ear and labyrinth disorders:

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

Renal and urinary disorders:

Common: urinary incontinence

Uncommon: renal failure

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

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:

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

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

Respiratory, thoracic and mediastinal disorder:

Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

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

Rare: myelodysplastic syndrome

Paediatric population

The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population.

There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of

pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

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

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

Symptoms may however be variable, and seizures have been reported in the presence of very high plasma levels (see section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Management

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

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Sodium valproate is an anticonvulsant.

The most likely mode of action for Sodium valproate injection is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the

further synthesis or further metabolism of GABA.

Clinical safety

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

5.2 Pharmacokinetic properties

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

Distribution

The percentage of free (unbound) drug is usually between 6 – 15% of 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 4.6)

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

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

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.

Special populations

Renal insufficiency

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

Paediatric population

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

5.3 Preclinical safety data

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

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

Reproductive and developmental toxicity

Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.

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

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

Testicular toxicity

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations is unknown, however body-surface-area comparisons indicate that there may be no safety margin.

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

considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin for the effect on testicular weight.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium Edetate

Hydrochloric Acid (for pH adjustment)

Sodium Hydroxide (for pH adjustment)

Water for Injections

6.2 Incompatibilities

Sodium Valproate Injection should not be administered via the same line as other IV additives (see section 4.2).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

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

After dilution

The contents of the vial should be used immediately or within 24 hours, to be stored at 2 to 8ºC.

Chemical and physical in-use stability has been demonstrated for four days at 25°C. From a microbiological point of view, the product should be used immediately after opening. 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°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Keep the vial in the outer carton to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Sodium valproate Advagen solution for injection or infusion is supplied as either 300mg/3ml or 400mg/4ml in Type I glass vial, with grey bromobutyl rubber stopper and aluminum seal with flip-off, coloured, plastic disc cap.

6.6 Special precautions for disposal and other handling

For infusion, the product may be diluted in 0.9% saline or 5% dextrose. Tests with the recommended infusion solutions over four days at 25ºC show compatibility. See also section 6.3.

Prior to use sodium valproate solution for injection and the diluted solution should be visually inspected. Only clear solutions without particles should be used.

The contents of the vial are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7 PRODUCT OWNER

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8 DATE OF REVISION OF THE TEXT

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