1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

NAVALPRO 400 mg/4 ml has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the foetus resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities.
Exposure to NAVALPRO 400 mg/4 ml *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD). NAVALPRO 400 mg/4 ml treatment should be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy and NAVALPRO 400 mg/4 ml should not be prescribed if the relevant Risk Minimisation Measures/Pregnancy Prevention Programme, cannot be implemented and supervised and patients are not committed to adhere to these measures (see sections 4.4 and 4.6).

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NAVALPRO 400 mg/4 ml powder and solvent for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of NAVALPRO 400 mg/4 ml contains 400 mg freeze-dried sodium valproate.

Each ampoule of NAVALPRO 400 mg/4 ml contains 4 ml sterile water for injection.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution

NAVALPRO 400 mg/4 ml :

Vial: A white lyophilised powder.

Ampoule: A transparent and colourless liquid.

Reconstituted solution: A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NAVALPRO 400 mg/4 ml is indicated:

In the treatment of generalised 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 generalised seizures
- specific syndromes (West, Lennon-Gastaut).

NAVALPRO 400 mg/4 ml is indicated for whom oral therapy is temporarily not possible.

4.2 Posology and method of administration

Posology

Adults and adolescents

Replacement for oral therapy:

Patients already satisfactorily treated with oral sodium valproate should continue at their current daily dose using continuous or repeated infusion, administered at the same frequency as the oral dose.

Initial exposure to NAVALPRO 400 mg/4 ml:

Patients may be given a slow intravenous injection over 3 to 5 minutes, usually 400 mg to 800 mg depending on body mass (up to 10 mg/kg) by slow intravenous injection over 3 to 5 minutes, usually followed by continuous or repeated infusion up to a maximum of 2 500 mg/day, or one other anti-epileptic medicine may be added at a low dosage.

Combination therapy:

When starting NAVALPRO 400 mg/4 ml in patients already on other anticonvulsants, these should be tapered slowly; initiation of NAVALPRO 400 mg/4 ml therapy should then be gradual, with target dose being reached after about 2 weeks. It may be necessary to increase the dose by 5 to 10 mg/kg/day when NAVALPRO 400 mg/4 ml is used with other anticonvulsants which induce liver enzymes, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn, or if side effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of NAVALPRO 400 mg/4 ml. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced and that of NAVALPRO 400 mg/4 ml increased. Dosage of both NAVALPRO 400 mg/4 ml and other medicines should be adjusted during the stabilization period to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with NAVALPRO 400 mg/4 ml alone.

Special populations

Elderly population

Although the pharmacokinetics of NAVALPRO 400 mg/4 ml is altered in the elderly, this is of 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 medicine is increased. This will affect the clinical interpretation of plasma valproate levels.

Renal impairment

It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5).

Paediatric population

Children dose (≥ 20 kg)

This is usually in the range of 20 to 30 mg/kg of body mass per day.

Initial dosage should be 400 mg/day irrespective of mass, in divided doses, with spaced dose increases until control is achieved. Where adequate control is not achieved within the above range, the dose may be increased to 35 mg/kg body mass per day.

Children dose < 20 kg:

20 mg/kg of body mass per day; in severe cases, this may be increased but only in patients in whom plasma NAVALPRO 400 mg/4 ml levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Method of administration

Intravenous injection.

Patients should be switched to an oral medicine as soon as is clinically feasible.

The concentration of NAVALPRO 400 mg/4 ml in plasma that appears to be associated with therapeutic effects is approximately 40 to 100 µg/ml. A method of measuring plasma levels is available. Therapeutic NAVALPRO 400 mg/4 ml plasma levels do not imply optimal seizure control; therefore, the optimal NAVALPRO 400 mg/4 ml dosage for a particular patient is mainly determined by seizure control. NAVALPRO 400 mg/4 ml plasma levels may however be helpful where there is poor seizure control or when side effects are suspected.

To reconstitute NAVALPRO 400 mg/4 ml, add the solvent provided (4 ml of Water for Injection) to the vial, allow it to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.
NAVALPRO 400 mg/4 ml may be given either by direct slow intravenous injection or by infusion using a separate intravenous line in 0,9 % sodium chloride, dextrose 5 %, or dextrose saline.

NAVALPRO 400 mg/4 ml should be reconstituted immediately prior to use, and as an infusion, should be used within 24 hours if stored in a fridge (5 °C ± 3 °C) or within 8 hours if stored at room temperature (25 °C). Discard any unused portion.

The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

4.3 Contraindications

NAVALPRO 400 mg/4 ml is contraindicated in:

- Patients with hypersensitivity to NAVALPRO 400 mg/4 ml or to any excipients in NAVALPRO 400 mg/4 ml (see section 6.1).
- Pregnancy and lactation (see sections 4.4 and 4.6).

  With the treatment of epilepsy:

  - In pregnancy, unless there is no suitable alternative treatment.

- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.

- Active liver disease, including the following:
  - Acute and chronic hepatitis.
  - Personal or family history of severe hepatic dysfunction especially medicine related.
  - Hepatic porphyria.
- Patients with known urea cycle disorders (see section 4.4).
- 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

Treatment with NAVALPRO 400 mg/4 ml should be initiated and supervised by a medical practitioner experienced in the management of epilepsy.

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

Female children, women of childbearing potential and pregnant women:

NAVALPRO 400 mg/4 ml has a high teratogenic potential and children exposed *in utero* to NAVALPRO 400 mg/4 ml have a high risk for congenital malformations and neurodevelopmental

disorders (see section 4.6).

NAVALPRO 400 mg/4 ml is contraindicated in the following situations:

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

Conditions of Pregnancy Prevention Programme:

The healthcare provider 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 NAVALPRO 400 mg/4 ml *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 NAVALPRO 400 mg/4 ml.
- The patient understands the need for regular (at least annual) review of treatment by a doctor experienced in the management of epilepsy.
- The patient understands the need to consult her doctor 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 doctor in case of pregnancy.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with NAVALPRO 400 mg/4 ml use.

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

Female children

The health care provider must ensure that:

- The parents/caregivers of female children understand the need to contact the doctor once the female child using NAVALPRO 400 mg/4 ml experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information regarding 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 doctor must annually reassess the need for valproate, as in NAVALPRO 400 mg/4 ml, therapy and consider alternative treatment options. If valproate, as in NAVALPRO 400 mg/4 ml, 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 doctor to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate, as in NAVALPRO 400 mg/4 ml. Treatment with NAVALPRO 400 mg/4 ml 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, as in NAVALPRO 400 mg/4 ml, must use effective contraception without interruption during the entire duration of treatment with NAVALPRO 400 mg/4 ml. 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 medicines

Concomitant use with oestrogen-containing medicines, 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 medicines.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives containing oestrogen/progestogen or progestogen only.

Annual treatment reviews by a specialist

The specialist should review at least annually whether valproate, as in NAVALPRO 400mg/4 ml is the most suitable treatment for the patient.

Pregnancy planning

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess valproate, as in NAVALPRO 400 mg/4 ml 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, as in NAVALPRO 400 mg/4 ml for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using valproate, as in NAVALPRO 400 mg/4 ml becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with valproate, as in NAVALPRO 400 mg/4 ml and consider alternative treatment options. The patients exposed to valproate, as in NAVALPRO 400 mg/4 ml, during pregnancy and their partners should be referred to a specialist experienced in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:

- The patient is made aware of the fact that valproate, as in NAVALPRO 400 mg/4 ml, can seriously harm their unborn baby every time valproate is dispensed.
- Patients are advised not to stop valproate, as in NAVALPRO 400 mg/4 ml medicine and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare providers and patients in avoiding exposure to valproate, as in NAVALPRO 400 mg/4 ml, during pregnancy, educational materials has been provided to reinforce the warnings, provide guidance regarding use of valproate, as in NAVALPRO 400 mg/4 ml, in women of childbearing potential and provide details of the Pregnancy Prevention Programme. Valproate, as in NAVALPRO 400 mg/4 ml, therapy should only be continued after a reassessment of the benefits and

risks of the treatment with NAVALPRO 400 mg/4 ml for the patient by a doctor experienced in the management of epilepsy.

Adult males intending procreation:

Valproate, as contained in NAVALPRO 400 mg/4 ml, has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see sections 4.6 and 4.8). The medical practitioner should discuss with adult males their intent to procreate, when prescribing NAVALPRO 400 mg/4 ml. If procreation is intended, NAVALPRO 400 mg/4 ml should be used only if alternative treatment options are not suitable.

Pancreatitis

Discontinue NAVALPRO 400 mg/4 ml if patient develops pancreatitis as it may be life-threatening. 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 decreased with increasing age. Severe seizures, neurological impairment or combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome (see section 4.8).

Liver dysfunction

Severe liver damage, including hepatic failure sometimes resulting in fatalities, have been reported. This usually occurs in children under the age of three years who are taking other anticonvulsants and those patients with severe seizure disorders, organic brain disease and (or) congenital metabolic or degenerative disease associated with mental retardation are at highest risk. 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 those children under 3 years of age due to the risk of liver toxicity.

Additionally, salicylates should not be used in children under 16 years.

Monotherapy is recommended in children under the age of 3 years when prescribing NAVALPRO 400 mg/4 ml, but the potential benefit of NAVALPRO 400 mg/4 ml 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 to 12 weeks.

Suggestive signs of liver dysfunction

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:

- 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 (see section 4.8).
- in patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of NAVALPRO 400 mg/4 ml. Patients (or their family for children) should be instructed to report immediately any such signs to a healthcare provider should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection of liver dysfunction

Liver function tests should be carried out before therapy (see section 4.3), and periodically monitored during the first 6 months of therapy, especially in patients 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 NAVALPRO 400 mg/4 ml 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 medicines, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

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

Aggravated convulsions

As with other anti-epileptic medicines, 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 NAVALPRO 400 mg/4 ml.

Confusion; cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate, as in NAVALPRO 400 mg/4 ml, therapy; they may be 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 have most often been reported during combined therapy (in particular with phenobarbitone) or after a sudden increase in valproate, as in NAVALPRO 400 mg/4 ml, doses. Cases of reversible dementia associated with cerebral atrophy have

been reported. Reversible Parkinsonism has been reported. Transient and (or) dose related fine postural tremor and somnolence have often been reported.
In case of aggravated convulsions, the patients should be advised to consult their doctor immediately (see section 4.8).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines. Data shows that anti-epileptic medicine 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, as in NAVALPRO 400 mg/4 ml.
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 medicines

The concomitant use of NAVALPRO 400 mg/4 ml and carbapenem medicine is not recommended (see section 4.5)

Patients with known or suspected mitochondrial disease

NAVALPRO 400 mg/4 ml may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor

regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Hypoalbuminaemia

Hypoalbuminaemia, as serum levels of NAVALPRO 400 mg/4 ml may increase.

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).

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 NAVALPRO 400 mg/4 ml.

Renal insufficiency

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

There have been reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function) associated with valproate, as in NAVALPRO 400 mg/4 ml, therapy but the mode of action is as yet unclear.

Systemic lupus erythematosus

Immune disorders have been noted during the use of valproate, as in NAVALPRO 400 mg/4 ml, and the potential benefit of NAVALPRO 400 mg/4 ml should be weighed against its potential risk in patients with systemic lupus erythematosus (see section 4.8).

Weight gain

Valproate, as in NAVALPRO 400 mg/4 ml, 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, as in NAVALPRO 400 mg/4 ml 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)

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when NAVALPRO 400 mg/4 ml is administered.

Alcohol

Alcohol intake is not recommended during treatment with NAVALPRO 400 mg/4 ml.

Paediatric population

Children (male and female) less than 18 years of age:

Epilepsy:

Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving NAVALPRO 400 mg/4 ml (see section 4.8). Current evidence is inconclusive as to the

possibility of harm to reproductive organs, skeletal system growth or developing brain of patients less than 18 years of age.

In male children less than 18 years of age, NAVALPRO 400 mg/4 ml should be used with caution and in alignment with guidelines on the use of antiepileptics.

NAVALPRO 400 mg/4 ml can be used in female children less than 18 years of age only if there is no suitable safer alternative therapy or alternate therapy have failed to control the epilepsy. In addition, for female children, ensure that the conditions of the pregnancy prevention programme are met (see sections 4.4 and 4.6).

4.5 Interaction with other medicines and other forms of interaction

Effects of NAVALPRO 400 mg/4 ml on other medicines

Antipsychotics, monoamine oxidase inhibitors (MAOIs), antidepressants and benzodiazepines.

NAVALPRO 400 mg/4 ml may potentiate the effect of other psychotropics such as antipsychotics, MAOIs, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

Neuroleptics, MAOIs, and other antidepressants may result in increased CNS depression and a lowering of the seizure threshold. Benzodiazepine may result in increased CNS depression.

In particular, adding olanzapine to valproate, as in NAVALPRO 400 mg/4 ml 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.
Clonazepam may produce absence status epilepticus in patients with a history of absence type seizures.

Lithium

NAVALPRO 400 mg/4 ml has no effect on serum lithium levels.

Olanzapine

NAVALPRO 400 mg/4 ml may decrease the olanzapine plasma concentration.

Phenobarbitone

NAVALPRO 400 mg/4 ml increases phenobarbitone 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 phenobarbitone doses if sedation occurs and determination of phenobarbitone plasma levels when appropriate.

Primidone

NAVALPRO 400 mg/4 ml 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

NAVALPRO 400 mg/4 ml decreases phenytoin total plasma concentration. Moreover NAVALPRO 400 mg/4 ml increases phenytoin free form with possible overdose symptoms (valproic acid, as in NAVALPRO 400 mg/4 ml, 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.

Phenytoin is an enzyme inducer and therefore decreases serum levels of NAVALPRO 400 mg/4 ml.

Carbamazepine

Clinical toxicity has been reported when NAVALPRO 400 mg/4 ml was administered with carbamazepine as valproate, as in NAVALPRO 400 mg/4 ml, may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Carbamazepine is an enzyme inducer and therefore decreases serum levels of NAVALPRO 400 mg/4 ml.

Lamotrigine

Lamotrigine metabolism is inhibited by NAVALPRO 400 mg/4 ml and and increases the lamotrigine mean half-life by nearly two fold. This interaction may lead to increased toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended, and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

Felbamate

NAVALPRO 400 mg/4 ml may decrease the felbamate mean clearance by up to 16 %.

Rufinamide

NAVALPRO 400 mg/4 ml may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of NAVALPRO 400 mg/4 ml. Caution should be exercised, in particular in children, as this effect is larger in this population.

Propofol

NAVALPRO 400 mg/4 ml may lead to an increased blood level of propofol. When co-administered with NAVALPRO 400 mg/4 ml, a reduction of the dose of propofol should be considered.

Zidovudine

NAVALPRO 400 mg/4 ml may raise zidovudine plasma concentration leading to increase zidovudine toxicity.

Nimodipine

In patients concomitantly treated with sodium valproate, as in NAVALPRO 400 mg/4 ml and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

Vitamin K-dependent anticoagulants

Anticoagulants and thrombolytic medicines may increase the risk of haemorrhage.

Close monitoring of INR should be performed in case of concomitant use of vitamin K dependent factor anticoagulants (e.g. warfarin and other coumarin anticoagulants) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by NAVALPRO 400 mg/4 ml. The prothrombin time should be closely monitored.

Temozolomide

Co-administration of temozolomide and NAVALPRO 400 mg/4 ml may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Salicylates

Salicylates should not be used concomitantly with sodium 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).

Effects of other medicines on NAVALPRO 400 mg/4 ml

Anti-epileptics

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbitone, carbamazepine) decrease valproate serum concentrations.

Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

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

Felbamate

The combination of felbamate and NAVALPRO 400 mg/4 ml decreases NAVALPRO 400 mg/4 ml clearance by 22 % to 50 % and consequently increase the valproate plasma concentrations. NAVALPRO 400 mg/4 ml dosage should be monitored.

Antimalarial medicines: Mefloquine, chloroquine

Mefloquine and chloroquine increase the valproate metabolism and may lower the seizure threshold and reduces the serum concentration of NAVALPRO 400 mg/4 ml. Therefore, epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of NAVALPRO 400 mg/4 ml may need adjustment.

Aspirin

In case of concomitant use of NAVALPRO 400 mg/4 ml and highly protein bound medicines (e.g. aspirin), valproate free serum levels may be increased.

Cimetidine and erythromycin

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

Carbapenem antibiotics (imipenem/meropenem/ertapenem/panipenem)

Decrease in valproate blood level have been reported when it is co-administered with carbapenem medicines resulting in a 60 % to 100 % decrease in valproate levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem medicines in patients stabilised on valproate, as in NAVALPRO 400 mg/4 ml should be avoided (see section 4.4). If these antibiotics have to be administered and cannot be avoided, close monitoring of valproate blood level is recommended.

Protease inhibitors

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

Colestyramine

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

Rifampicin

Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, NAVALPRO 400 mg/4 ml dosage adjustment may be necessary when it is co-administered with rifampicin.

Quetiapine

Co-administration of NAVALPRO 400 mg/4 ml and quetiapine may increase the risk of neutropenia/leucopenia.

Hormonal contraception (Oestrogen-containing medicines, 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 medicines in women receiving hormonal contraception.

NAVALPRO 400 mg/4 ml usually has no enzyme-inducing effect; as a consequence, NAVALPRO 400 mg/4 ml does not reduce efficacy of oestrogen and/or progestogen containing medicines in women receiving hormonal contraception, including the oral contraceptive pill.

Other interactions

Caution is advised when using NAVALPRO 400 mg/4ml 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 medicines, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Urine tests for diabetics

NAVALPRO 400 mg/4 ml is excreted by the kidneys as ketones and this may give false positive results in urine tests for diabetics (see section 4.4).

4.6 Fertility, pregnancy and lactation

- **NAVALPRO 400 mg/4 ml is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.**
- **NAVALPRO 400 mg/4 ml is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and section 4.4).**

Women of childbearing potential and female children

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).

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4).

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

Pregnancy

Teratogenicity and developmental effects

Pregnancy exposure risk related to NAVALPRO 400 mg/4 ml

Both NAVALPRO 400 mg/4 ml monotherapy and NAVALPRO 400 mg/4 ml polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including

valproate, as in NAVALPRO 400 mg/4 ml, is associated with a greater risk of congenital malformations than valproate, as in NAVALPRO 400 mg/4 ml, monotherapy.

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

Congenital malformations

Data has shown that 10,73 % of children of epileptic women exposed to valproate, as in NAVALPRO 400 mg/4 ml monotherapy during pregnancy suffer from congenital malformations. This is a greater risk of major malformations than for the general population, for whom the risk is about 2 % to 3 %. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Data shows 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.

Developmental disorders

Data have shown that exposure to valproate, as in NAVALPRO 400 mg/4 ml *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. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

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

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure *in utero* was on average 7 to 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, as in NAVALPRO 400 mg/4 ml 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.

Oestrogen-containing medicines
Oestrogen-containing medicines, 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 section 4.4 and 4.5).

If a woman plans a pregnancy
If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess valproate, as in NAVALPRO 400 mg/4 ml, 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 NAVALPRO 400 mg/4 ml for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

NAVALPRO 400 mg/4 ml as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see section 4.3 and 4.4). If a woman using valproate, as in NAVALPRO 400 mg/4 ml, 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, as in NAVALPRO 400 mg/ 4 ml, in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive NAVALPRO 400 mg/ 4 ml for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of NAVALPRO 400 mg/ 4 ml into several small doses to be taken throughout the day.
- The use of a prolonged release tablet formulation may be preferable to other treatment formulations, including NAVALPRO 400 mg/ 4 ml, in order to avoid high peak plasma concentrations.

All patients with NAVALPRO 400 mg/4 ml-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate, as in NAVALPRO 400 mg/4 ml exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported in neonates whose mothers have used sodium valproate, as in NAVALPRO 400 mg/4 ml, during pregnancy. This haemorrhagic syndrome is related to thrombocytopaenia, hypofibrinogenaemia and/or to a decrease in other coagulation factors. Afibrinogenaemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone 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, as in NAVALPRO 400 mg/4 ml during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate, as in NAVALPRO 400 mg/4 ml, 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, as in NAVALPRO 400 mg/4 ml, during the last trimester of their pregnancy.

Breastfeeding

NAVALPRO 400 mg/4 ml is contraindicated in breastfeeding mothers. When given to breastfeeding mothers, sodium valproate as in NAVALPRO 400 mg/4 ml, is excreted in breast milk. Concentrations of NAVALPRO 400 mg/4 ml in breast milk have been found to be 1 % to 10 % of total maternal serum concentration.

Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8). A decision must be made whether to discontinue breastfeeding or to discontinue/abstain

from NAVALPRO 400 mg/4 ml therapy considering the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, menstrual disorders, polycystic ovaries and increased testosterone levels have been reported in women using valproate, as in NAVALPRO 400 mg/4 ml (see section 4.3). NAVALPRO 400 mg/4 ml administration may also impair fertility in men (see section 4.3). Data indicate that fertility dysfunctions are reversible after treatment discontinuation.

Very low concentrations of valproate have been detected in semen of males on treatment with valproate, as contained in NAVALPRO 400 mg/4 ml.

It is not known with certainty if fertility would be affected by NAVALPRO 400 mg/4 ml treatment in children less than 18 years of age, as valproate may interact with sex hormones (see section 4.4).

4.7 Effects on ability to drive and use machines

NAVALPRO 400 mg/4 ml has moderate influence on the ability to drive and use machines.

Since adverse reactions such as dizziness and visual disturbances have been reported in patients receiving NAVALPRO 400 mg/ml, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that NAVALPRO 400 mg/4 ml does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a) *Summary of the safety profile*

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

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Myelodysplastic syndrome	
Blood and the lymphatic system disorders	Thrombocytopenia, anaemia	Reversible prolongation of bleeding time, leucopenia, pancytopenia, bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis	
Immune system disorders	Hypersensitivity	Allergic reactions, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme	
Endocrine disorders		Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase) hypothyroidism	
Metabolism and nutrition disorders	Weight gain, hyponatraemia	Hyperammonaemia, obesity	
Psychiatric disorders	Confusional state, hallucinations, aggression, agitation, disturbance in attention		
Nervous system disorders	Tremor, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness may occur within a few minutes	Sedation, ataxia, lethargy, encephalopathy, coma, reversible parkinsonism, paraesthesia, aggravated convulsions, reversible dementia associated with reversible cerebral atrophy, cognitive disorder	

	and it usually resolves spontaneously within a few minutes		
Eye disorders		Diplopia	
Ear and labyrinth disorders	Deafness (a cause and effect relationship has not been established)	Hearing loss, either reversible or irreversible	
Vascular disorders	Haemorrhage	Oedema, vasculitis	
Respiratory, thoracic and mediastinal disorders		Pleural effusion	
Gastrointestinal disorders	Increased appetite, nausea (occurs a few minutes after intravenous injection with spontaneous resolution within a few minutes), gastralgia, diarrhoea, vomiting, constipation, gingival disorder (mainly gingival hyperplasia), stomatitis	Pancreatitis (sometimes lethal), polydipsia	
Hepato-biliary disorders	Transient elevation of liver enzymes (15 to 30 % of patients), liver injury	Liver dysfunction, severe liver damage, including hepatic failure	
Skin and subcutaneous tissue disorders	Transient and/or dose related alopecia (hair loss), nail and nail bed	Rash, diaphoresis, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth), angioedema. toxic epidermal necrolysis, Drug Rash with Eosinophilia and	

	disorders	Systemic Symptoms (DRESS) syndrome	
Musculoskeletal and connective tissue disorders		Bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with valproate, as in NAVALPRO 400 mg/4 ml. The mechanism by which valproate, as in NAVALPRO 400 mg/4 ml affects bone metabolism has not been identified. Systemic lupus erythematosus, rhabdomyolysis	
Renal and urinary disorders	Urinary incontinence	Reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria), polyuria, enuresis, renal failure, tubulointerstitial nephritis; renal failure	
Reproductive system and breast disorders	Dysmenorrhea	Irregular periods, amenorrhoea, gynaecomastia, male infertility, polycystic ovaries, impairment of ovarian function and of fertility in females	
Congenital and familial and genetic disorders			Teratogenicity (see section 4.6)
General disorders and administrative site conditions		Hypothermia, non-severe peripheral oedema	Inflammatory reactions and pain at the site of injection
Investigations		Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged), hypothermia, non-severe peripheral oedema	

c) *Description of selected adverse reactions*

Blood and lymphatic system disorders

The blood picture returned to normal when the medicine 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 (NAVALPRO 400 mg/4 ml has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of NAVALPRO 400 mg/4 ml pending investigations (see section 4.6). Monitor platelet function before major surgery.

Metabolism and nutritional disorders

Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.6).

Hyperammonaemia

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 NAVALPRO 400 mg/4 ml should be discontinued.

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

Nervous system disorders

Tremor, 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.

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 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-convulsant, notably phenobarbitone 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.

Gastrointestinal disorders

The frequent listed adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment.

Hepato-biliary disorders

Liver dysfunction, severe liver damage, including hepatic failure. This usually occurs within the first few months of treatment and in children under the age of three years receiving other anticonvulsants. Discontinue therapy with NAVALPRO 400 mg/4 ml (see section 4.3).

Skin and subcutaneous tissue disorders

Transient and/or dose related alopecia (hair loss)

Regrowth normally begins within six months, although the hair may become curlier than previously.

Hair disorder

Such as abnormal hair texture, hair colour changes, abnormal hair growth

d) Paediatric population

Psychiatric disorders

Abnormal behaviour, psychomotor hyperactivity, learning disorder.

These ADRs are principally observed in the paediatric population.

Reporting of suspected adverse reactions

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

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, the only likely symptoms are nausea, vomiting and dizziness. Clinical signs of acute massive overdose, i.e. plasma concentration of 10 to 20 times the maximum therapeutic levels, usually include CNS depression or a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. Symptoms may however be variable, and seizures have been reported in Ref 1, Page 23, Line 8-9 e of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in NAVALPRO 400 mg/4 ml may lead to hypernatraemia when taken in overdose.

Treatment

Treatment is symptomatic and supportive. Hospital management of overdose should be symptomatic: gastric lavage (which is useful up to 10 to 12 hours following ingestion), cardio-respiratory monitoring, assisted ventilation and other supportive measures are recommended. Haemodialysis and haemoperfusion have been used successfully.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants including anti-epileptics

Pharmacotherapeutic group: Central nervous system depressants

ATC code: N03AG01

Mechanism of action

Sodium valproate has anticonvulsant properties. The mechanism of action is not fully understood but it is thought to be due to a direct or secondary increase in the concentration of gamma-aminobutyric acid (GABA) caused either by decreased metabolism or decreased reuptake in brain tissues.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentration is reached at the end of a 1-hour intravenous infusion. Sodium valproate bioavailability is close to 100 % following IV administration.

Distribution

Protein binding is usually high (90 to 95 %) but decreases as the serum concentration increases. It is also decreased in the elderly, in patients with chronic hepatic diseases and in renal impairment. Sodium valproate is distributed in the cerebrospinal fluid and the concentration is similar to that of the unbound concentration in plasma. It is also distributed into breast milk (1 % to 10 % of maternal serum concentrations). The percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels. The pharmacological (or therapeutic) effects of valproic acid are not clearly correlated with the total or free (unbound) plasma valproic acid levels.

Biotransformation

The reported effective therapeutic range for plasma valproic acid levels in epilepsy is considered to be between 30 and 100 µg/ml. Sodium valproate is primarily metabolised in the liver, with some of the metabolites having anticonvulsant activity.

Elimination

The elimination half-life is variable but is approximately 16 hours after intravenous infusion of 1 000 mg over 1 hour. It is usually shorter in children. It is renally excreted mainly as the glucuronide conjugate and beta-oxidation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2. Incompatibilities

It should not be administered via the same IV line as other IV additives.

6.2 Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 °C.

From a microbiological point of view, the solutions must be used immediately after reconstitution, and other conditions of use are the responsibility of the user and should not be more than 24 hours in a fridge, unless controlled and validated aseptic conditions are applied.

Keep the vial and ampoule in the outer carton, until required for use.

6.5 Nature and contents of container

1 x 20 ml transparent and colourless Type I glass vial containing a white lyophilised powder with an aluminium seal, chlorobutyl rubber stopper, and a plastic flip off cap.

1 x transparent and colourless Type I glass ampoule containing a solvent.

Both the vial and ampoule are packed together in a plastic tray and in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

A40/2.5/0342

~~9~~ DATE OF FIRST AUTHORISATION

07 December 2012

10 DATE OF REVISION OF TEXT

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Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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