1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINE FOR HUMAN USE

NAVALPRO LIQUID 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 LIQUID *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD). NAVALPRO LIQUID treatment should be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy and NAVALPRO LIQUID 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 LIQUID 200 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of NAVALPRO LIQUID contains 200 mg sodium valproate.

Preservatives:

Sodium methyl parahydroxybenzoate 0,1 % *m/v*

Sodium propyl parahydroxybenzoate 0,04 % *m/v*

Contains sweeteners:

Saccharin sodium 4 mg

Liquid sorbitol 1 750 mg

Sorbitol is a source of fructose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Liquid.

NAVALPRO LIQUID is a clear, red coloured liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NAVALPRO LIQUID is indicated in children, adolescents and adults for:

- the treatment of generalised epilepsy, particularly with the following patterns of seizures:
    - absence,
    - myoclonic,
    - tonic-clonic,
    - atonic,
    - mixed.
- the treatment of partial epilepsy:
    - simple or complex seizures,
    - secondary generalised seizures,
    - specific syndromes (West, Lennox-Gastaut).

4.2. Posology and method of administration

Posology

Daily dosage requirements vary according to age

and body weight.

Adults

Dosage should start at 600 mg/day, where applicable in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range of 1 000 to 2 000 mg/day (i.e. 20 to 30 mg/kg body mass). If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day, or one other anti-epileptic medicine may be added at a low dosage. In patients already receiving other therapy, the same pattern should be followed.

If increased sedation is observed, dosage of barbiturates or benzodiazepines (e.g. lorazepam) should be reduced as that of NAVALPRO LIQUID is increased; dosage of both NAVALPRO LIQUID and other medicines should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with NAVALPRO LIQUID alone.

Paediatric population

Children over 20 kg

Initial dosage should be 400 mg/day irrespective of mass, where applicable in divided doses, with spaced increases until control is achieved. This is usually within the range of 20 to 30 mg/kg of body mass per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per day.

Children under 20 kg

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

Combined therapy

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

General considerations

The concentration of valproate in plasma that appears to be associated with therapeutic effects is approximately 30 to 100 µg/mL. 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).

Special populations

Elderly population

Although the pharmacokinetics of NAVALPRO LIQUID is modified 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 valproic acid levels.

Renal insufficiency

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 5.2).

Method of administration

For oral administration.

NAVALPRO LIQUID should preferably be taken with or after food.

NAVALPRO LIQUID should not be diluted. NAVALPRO LIQUID should be given in divided doses.

4.3. Contraindications

NAVALPRO LIQUID is contraindicated in:

- Patients with hypersensitivity to sodium valproate or to any excipients in NAVALPRO LIQUID (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 (see sections 4.4 and 4.6).
- Active liver disease, including:
    - acute hepatitis,
    - chronic hepatitis,
    - personal or family history of 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 (see section 4.4).
- 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 LIQUID should be initiated and supervised by a medical practitioner experienced in the management of epilepsy.

Female children, women of childbearing potential and pregnant women

Pregnancy Prevention Programme

Valproate, as in NAVALPRO LIQUID, has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

NAVALPRO LIQUID 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 neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

• The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

• The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.

• The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.

• The patient understands the need to consult her medical practitioner 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 medical practitioner in case of pregnancy.

• The patient has received the Patient Information Leaflet.

• 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 NAVALPRO LIQUID experiences menarche.

• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to NAVALPRO LIQUID *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 NAVALPRO LIQUID 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 NAVALPRO LIQUID. Treatment with NAVALPRO LIQUID 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 NAVALPRO LIQUID 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 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 NAVALPRO LIQUID 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 NAVALPRO LIQUID 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 NAVALPRO LIQUID for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using NAVALPRO LIQUID becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with NAVALPRO LIQUID and consider alternative treatment options. The patients with NAVALPRO LIQUID -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:

• The Patient Card is provided with every valproate dispensation and that patients understand its content.

• Patients are advised not to stop NAVALPRO LIQUID 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 NAVALPRO LIQUID during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate, as in NAVALPRO LIQUID, in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Information Leaflet and Patient Card should be provided to all women of childbearing potential using NAVALPRO LIQUID.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

NAVALPRO LIQUID 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.

Adult males intending procreation:

Valproate, as contained in NAVALPRO LIQUID, 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 LIQUID. If procreation is intended, NAVALPRO LIQUID should be used only if alternative treatment options are not suitable.

Liver dysfunction

Conditions of occurrence:

Cases of severe liver damage resulting sometimes in fatalities have been reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3, the incidence of occurrence is reduced and decreases with age.

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

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

The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.

Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

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 *Conditions of occurrence* above):

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

These are an indication for immediate withdrawal of NAVALPRO LIQUID.

Patients (or their family, in the case of children) should be instructed to report immediately any such signs to a medical practitioner should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be performed before 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 NAVALPRO LIQUID 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.

Increased liver enzymes may be noted with NAVALPRO LIQUID, particularly at the beginning of therapy.
More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis
Severe pancreatitis, which may result in fatalities, has been reported (see section 4.8). 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 anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

Cases of pancreatitis have been reported; therefore patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, NAVALPRO LIQUID should be interrupted.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. Anti-epileptic medicines have 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 contained in NAVALPRO LIQUID.

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.

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 LIQUID. In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

Withdrawal

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, as contained in NAVALPRO LIQUID, 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.

Carbapenems

The concomitant use of NAVALPRO LIQUID and carbapenem medicines is not recommended (see section 4.5).

Mitochondrial disease

NAVALPRO LIQUID may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded DNA Polymerase γ (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).

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

Since immune disorders have been only noted during the use of NAVALPRO LIQUID, the potential benefit of NAVALPRO LIQUID should be weighed against its potential risk in patients with systemic lupus erythematosus.

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.

Weight gain

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

NAVALPRO LIQUID is eliminated mainly through the kidneys, partly in the form of ketone bodies, and this may give false-positive readings 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 NAVALPRO LIQUID.

Alcohol

Alcohol intake is not recommended during treatment with NAVALPRO LIQUID.

Excipients

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicines for oral use, such as NAVALPRO LIQUID, may affect the bioavailability of other medicines for oral use administered concomitantly.

Patients with hereditary fructose intolerance (HFI) should not take/be given NAVALPRO LIQUID.

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 LIQUID (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 LIQUID should be used with caution and in alignment with guidelines on the use of antiepileptics.

NAVALPRO LIQUID 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 LIQUID on other medicines:

Neuroleptics, mono-amine oxidase inhibitors (MAOIs), antidepressants and benzodiazepines

NAVALPRO LIQUID may potentiate the effect of other psychotropics such as neuroleptics, MAOIs, antidepressants and benzodiazepines; therefore clinical monitoring is advised and dosage should be adjusted when appropriate.

Lithium

NAVALPRO LIQUID has no effect on serum lithium levels.

Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

Adding olanzapine to NAVALPRO LIQUID 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.

Quetiapine

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

Phenobarbitone

NAVALPRO LIQUID 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 LIQUID 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 LIQUID decreases phenytoin total plasma concentration. Moreover NAVALPRO LIQUID increases phenytoin free form with possible overdosage 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 NAVALPRO LIQUID 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

NAVALPRO LIQUID may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. The risk of rash may be increased by coadministration of lamotrigine with NAVALPRO LIQUID.

Felbamate

Valproic acid, as in NAVALPRO LIQUID, may decrease the felbamate mean clearance by up to 16 %.

Rufinamide

Valproic acid, as in NAVALPRO LIQUID, 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, as in NAVALPRO LIQUID, 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

NAVALPRO LIQUID may raise zidovudine plasma concentration leading to increased zidovudine
toxicity.

Nimodipine

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

Effects of other medicines on NAVALPRO LIQUID:

Antidepressants and neuroleptics may antagonise the anti-epileptic activity of NAVALPRO LIQUID by lowering the seizure threshold. This may require NAVALPRO LIQUID dosage adjustments.

Anti-epileptics

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbitone, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

Valproic acid 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.

Combination of felbamate and NAVALPRO LIQUID may increase valproate serum concentration. NAVALPRO LIQUID dosage should be monitored.

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

Anti-malarials

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy. Chloroquine may also lower the seizure threshold.

Accordingly, the dosage of NAVALPRO LIQUID may need adjustment.

Highly protein-bound medicines

In case of concomitant use of NAVALPRO LIQUID and highly protein bound medicines (aspirin), valproate free serum levels may be increased (see section 4.4).

Vitamin K dependent factor anticoagulants

Close monitoring of INR should be performed in case of concomitant use of vitamin K dependent factor anticoagulants (e.g. warfarin) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by NAVALPRO LIQUID.

Cimetidine or 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

Carbapenem antibiotics (imipenem/ meropenem/ ertapenem): decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

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.

Colestyramine

Colestyramine may decrease the absorption of valproate, and may lead to a decrease in plasma level of valproate, as in NAVALPRO LIQUID, when co-administered.

Other interactions:

NAVALPRO LIQUID usually has no enzyme inducing effect; as a consequence, NAVALPRO LIQUID does not reduce efficacy of oestrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

Topiramate or acetazolamide

Concomitant administration of valproate, as in NAVALPRO LIQUID, 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.

4.6. Fertility, pregnancy and lactation

NAVALPRO LIQUID is contraindicated as treatment for epilepsy during pregnancy and lactation, unless there is no suitable alternative to treat epilepsy. NAVALPRO LIQUID 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).

Women of childbearing potential

Female children and woman of childbearing potential (see above and sections 4.3 and 4.4)

Oestrogen-containing medicines

Oestrogen-containing medicines, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, as in NAVALPRO LIQUID, 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 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.

Pregnancy

Teratogenicity and developmental effects

Pregnancy exposure risk related to valproate, as in NAVALPRO LIQUID

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

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10,73 % of children of epileptic women exposed to valproate 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.

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

Developmental disorders

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

Studies in preschool children exposed *in utero* to valproate show that up to 30 % 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 that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate *in utero* are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
Limited data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Valproate, as in NAVALPRO LIQUID, 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 NAVALPRO LIQUID 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 LIQUID, in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive valproate for epilepsy, it is recommended to:

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

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

Risk in the neonate

Cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate, as in NAVALPRO LIQUID, during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia; 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 phenobarbitone and enzymatic inducers.

Hypofibrinogenemia is possibly associated with decrease of coagulation factors.

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 LIQUID, during the third trimester of their pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate, as in NAVALPRO LIQUID, 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 LIQUID, during the last trimester of their pregnancy.

Breastfeeding

Patients treated with NAVALPRO LIQUID should not breastfeed (see section 4.3).
NAVALPRO LIQUID crosses the placenta. When given to breastfeeding mothers, NAVALPRO LIQUID is excreted in breast milk.
Excretion of valproate in breast milk results in a concentration between 1 % and 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 breastfeeding or to discontinue/abstain from NAVALPRO LIQUID therapy.

Fertility

Amenorrhoea, menstrual disorders, polycystic ovaries and increased testosterone levels have been reported in women using valproate, as in NAVALPRO LIQUID (see section 4.8).
Valproate administration may also impair fertility in men (see section 4.8). Case reports 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 LIQUID.

It is not known with certainty if fertility would be affected by NAVALPRO LIQUID 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 LIQUID has moderate influence on the ability to drive and use machines.

Patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines (see section 4.5).

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that NAVALPRO LIQUID does not adversely affect their ability to do so safely (see section 4.8).

4.8. Undesirable effects

a) 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	Leucopenia, pancytopenia, reduction of fibrinogen, increase in bleeding time, bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis	
Immune system disorders		Allergic reactions, angioedema	
Endocrine disorders		Syndrome of Inappropriate Secretion of ADH	

		(SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase), hypothyroidism (see section 4.6)	
Metabolism and nutrition disorders	Hyponatraemia, increased weight[1], hyperammonaemia without change in liver function tests[2]	Obesity	
Psychiatric disorders	Confusional state, hallucinations, aggression[3], agitation[3], disturbance in attention	Abnormal behaviour[3], psychomotor hyperactivity[3], learning disorder[3], suicidal ideation or behaviour (class effect)	
Nervous system disorders	Tremor, extrapyramidal disorder, somnolence, memory impairment, headache, nystagmus	Stupor, lethargy, transient coma (encephalopathy), convulsions, reversible dementia associated with reversible cerebral atrophy, reversible parkinsonism, postural tremor, ataxia, paraesthesia, cognitive disorder, increase in alertness, aggression, hyperactivity, behavioural deterioration	
Eye disorders		Diplopia	
Ear and labyrinth disorders		Hearing loss, either reversible or irreversible	
Vascular disorders	Haemorrhage	Vasculitis	
Respiratory, thoracic and mediastinal disorders		Pleural effusion	
Gastrointestinal disorders	Nausea, gastralgia, diarrhoea, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis	Pancreatitis, which may be lethal (see section 4.4)	
Hepato-biliary disorders	Liver injury, severe liver damage and dysfunction, including hepatic failure which may resulting in	Liver dysfunction (see section 4.4)	

	death, increased liver enzymes		
Skin and subcutaneous tissue disorders	Transient and/or dose-related hair loss[4], hypersensitivity, nail and nail bed disorders	Cutaneous reactions such as exanthematous rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome	
Musculoskeletal and connective tissue disorders		Decreased bone mineral density, osteopenia, osteoporosis, fractures[5], systemic lupus erythematosus, rhabdomyolysis	
Renal and urinary disorders	Urinary incontinence	Renal failure, enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria)	
Reproductive system and breast disorders	Dysmenorrhea, male infertility, polycystic ovaries, gynaecomastia	Amenorrhoea, irregular periods, impairment of ovarian function and of fertility in females	
Congenital and familial and genetic disorders	See sections 4.4 and 4.6		Teratogenicity (see section 4.6)
General disorders and administrative site conditions		Non-severe peripheral oedema, hypothermia	
Investigations		Decreased coagulation factors (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated	

		partial prolonged thromboplastin time, prolonged thrombin time, prolonged INR)	

1: Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome.

2: Should not cause treatment discontinuation. May occur with neurological symptoms.

3: Principally observed in the paediatric population.

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

5: May occur upon long-term use of valproate, as in NAVALPRO LIQUID.

b) Description of selected adverse reactions

Gastrointestinal disorders

The 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 NAVALPRO LIQUID with or after food.

Nervous system disorders

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 phenobarbitone or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

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, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of overdose usually include CNS depression, 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 the presence of high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

Treatment

Hospital management of overdose should be symptomatic:

cardio-respiratory monitoring, assisted ventilation and other supportive measures are recommended. Haemodialysis and haemo-perfusion have been used successfully.

Naloxone has been successfully used in a few cases.

Deaths have occurred following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Antiepileptics, fatty acid derivatives

ATC code: N03AG01

Mechanism of action

Sodium valproate has anticonvulsant properties. The exact mode of action is unknown. However, the most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

5.2. Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels in epilepsy is considered to be between 30 and 100 µg/mL. This reported range may depend on time of sampling and presence of co-medicines. 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.

In cases where measurement of plasma levels is considered necessary, trough plasma levels should be used for therapeutic monitoring.

Absorption and Distribution

Peak plasma concentrations are observed in 1 to 4 hours after sodium valproate liquid, but this can be delayed for several hours if valproic acid is administered in enteric-coated tablets, in prolonged release formulation, or is ingested with meals.

Sodium valproate bioavailability is close to 100 % following oral or IV administration.

Valproic acid concentration in cerebrospinal fluid is close to free plasma concentration.

Steady state plasma concentration is reached after 3 to 4 days, following oral administration.

Valproate is highly bound to plasma proteins; protein binding is dose-dependent and saturable.

Biotransformation

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

When given in therapeutic doses, most of the medicine is converted to the conjugate ester of glucuronic acid, while mitochondrial metabolism, principally by means of beta-oxidation, accounts for the remainder. Some of the metabolites have anticonvulsant activity.

Elimination

Sodium valproate is mainly excreted in urine following metabolism via glucuroconjugation and beta-oxidation.

Sodium valproate does not increase its own degradation neither that of other medicines such as oestrogen- and progestogen-containing medicines.

The elimination half-life of sodium valproate varies from approximately 8 to 20 hours. It is usually shorter in children.

Special populations

Renal impairment

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cherry flavour, concentrated hydrochloric acid (for pH-adjustment), hydroxyethyl cellulose, liquid sorbitol, ponceau 4R supra (E124), purified water, saccharin sodium, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

300 ml liquid in an amber coloured, glass bottle in a carton.

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

46/2.5/0796

9. DATE OF FIRST AUTHORISATION

26 July 2022

10. DATE OF REVISION OF TEXT

26 July 2022

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

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