1.3.1.1. PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

NAVALPRO CR 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 CR *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD).

NAVALPRO CR treatment must be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and NAVALPRO CR must 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 section 4.4 and 4.6).

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NAVALPRO CR 200 mg film-coated tablets

NAVALPRO CR 300 mg film-coated tablets

NAVALPRO CR 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NAVALPRO CR 200

Each film-coated controlled release tablet of NAVALPRO CR 200 contains 133,2 mg sodium valproate and 58,0 mg valproic acid, together equivalent to 200 mg sodium valproate.

Contains sweetener: Acesulfame potassium 2,40 mg.

NAVALPRO CR 300

Each film-coated controlled release tablet of NAVALPRO CR 300 contains 199,8 mg sodium valproate and 87,0 mg valproic acid, together equivalent to 300 mg sodium valproate.

Contains sweetener: Acesulfame potassium 3,60 mg.

NAVALPRO CR 500:

Each film-coated controlled release tablet of NAVALPRO CR 500 contains 333,0 mg sodium valproate and 145,0 mg valproic acid, together equivalent to 500 mg sodium valproate.

Contains sweetener: Acesulfame potassium 6,00 mg.

NAVALPRO CR 200, 300 & and 500 are sugar free.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

NAVALPRO CR 200 is a white oval film-coated tablets with dimensions of approximately 13,8 mm x 7,2 mm.

NAVALPRO CR 300 is a white oblong film-coated tablets with dimensions of approximately 16,7 mm x 6,7 mm and with a break mark on both sides.

NAVALPRO CR 500 is a white oblong film-coated tablets with dimensions of approximately 17,7 mm x 9,2 mm and with a break mark on both sides.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NAVALPRO CR indicated for:

- The treatment of generalised epilepsy, particularly with the following patterns of seizures:
    - absence
    - myoclonic
    - tonic-clonic
    - atonic
    - mixed

as well as, for partial epilepsy in:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut).

- The acute and maintenance treatment of manic episodes associated with bipolar disorders in adults.

4.2 Posology and method of administration

Posology

NAVALPRO CR is a controlled release formulation of valproate, which reduces peak concentration and ensures a more even plasma concentration throughout the day. NAVALPRO CR may be given once or twice daily.

Daily dosage requirements vary according to age and body mass.

In patients where adequate control has been achieved, NAVALPRO CR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Adults

Epilepsy

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 antiepileptic 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 CR is increased; dosage of both NAVALPRO CR 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 CR alone.

For the acute and maintenance treatment and of maniac episodes associated with bipolar disorders

The recommended initial dose is 1 000 mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effect.

Doses should be adjusted according to individual clinical response.

Maintenance treatment should be established individually with the lowest effective dose.

Combined therapy

When starting NAVALPRO CR in patients already on other anticonvulsants, these should be tapered slowly. Initiation of NAVALPRO CR therapy should then be gradual, with target dose being reached after about 2 weeks.

In certain cases it may be necessary to increase the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, e.g. phenytoin, phenobarbital 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 CR. When barbiturates are being administered concomitantly and particularly if sedation is observed, 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 **(65 years and older)**

Although the pharmacokinetics of NAVALPRO CR 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.

Elderly patients have lowered intrinsic clearances, indicating a reduction of valproate metabolising capacity and a fall in serum albumin.

These patients may also be more susceptible to certain adverse reactions, including somnolence. Therefore, these patients should receive a lower daily dosage, and the serum concentrations should be kept in the lower therapeutic range.

Renal insufficiency

It may be necessary to decrease the dosage. The dosage should be adjusted according to clinical monitoring, since plasma concentrations may be misleading (see section 5.2).

Paediatric population

The safety and efficacy of NAVALPRO CR in children has not been established.

Method of administration

For oral administration.

The tablets should be swallowed whole, if necessary with a little water (but not with aerated mineral water) and not crushed or chewed.

NAVALPRO CR should preferably be taken with or after food to reduce gastro-intestinal side effects.

4.3 Contraindications

- NAVALPRO CR is contraindicated in:
- Patients with hypersensitivity to sodium valproate or to any excipients in NAVALPRO CR (see section 6.1).
- Pre-existing liver disease or a family history of severe hepatic dysfunction, and active liver disease including:
  - Acute hepatitis
  - Chronic hepatitis
  - Personal or family history of severe hepatitis, especially if medicine-related
  - Hepatic porphyria
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG, e.g. Alpers-Huttenlocher Syndrome) (see section 4. 4).
- Patients with known urea cycle disorders (hyperammonaemic encephalopathy) (see section 4.4).
- Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).
- Concurrent use with MOAI (see section 4.5).
- Pregnancy and lactation (see section 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.

With the treatment of bipolar disorder:

- In pregnancy
- In women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled.
-

4.4 Special warnings and precautions for use

Treatment with NAVALPRO CR must be initiated and supervised by a medical practitioner experienced in the management of epilepsy and bipolar disorders.

Women of childbearing potential and pregnant women

Pregnancy Prevention Programme:

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

NAVALPRO CR is contraindicated in the following situations:

With treatment of epilepsy:

- in pregnancy, unless there is no suitable alternative treatment (see section 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.6).

With treatment of bipolar disorder:

- in pregnancy (see section 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.6)

Conditions of the Pregnancy Prevention Programme:

The medical practitioner must ensure that:

- individual circumstances are 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 NAVALPRO CR *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 “Contraception” in this section), without interruption during the entire duration of treatment with NAVALPRO CR.
- the patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy, or bipolar disorders.

- the patient understands the need to consult a medical practitioner as soon as she is planning pregnancy to ensure timeous 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 Guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with NAVALPRO CR use (Annual Risk Acknowledgement Form).

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

Pharmacists or healthcare professionals must ensure that:

- the Patient Card is provided with every NAVALPRO CR dispens~~ing~~ed and that the patients understand its content.
- patients are advised not to stop their NAVALPRO CR medicine and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Pregnancy test:

Pregnancy must be excluded before start of treatment with NAVALPRO CR. Treatment with NAVALPRO CR 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 CR must use effective contraception without interruption during the entire duration of treatment with NAVALPRO CR. 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, which includes a barrier method, should be used.

Individual circumstances should be evaluated in each case, when choosing the contraception method, and involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea she must follow all the advice on effective contraception (see section 4.3.).

Estrogen-containing medicines:

NAVALPRO CR does not reduce efficacy of hormonal contraceptives. However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased NAVALPRO CR efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (see section 4.5).

Annual treatment reviews by a medical practitioner:

The medical practitioner must at least annually review whether NAVALPRO CR is the most suitable treatment for the patient. The medical practitioner 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:

For the indication of epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess NAVALPRO CR 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 NAVALPRO CR risks for the unborn child, to support her informed decision-making regarding family planning (see section 4.3).

For the indication of bipolar disorder, if a woman is planning to become pregnant a medical practitioner experienced in the management of bipolar disorder must be consulted and treatment with NAVALPRO CR should be discontinued and, if needed, switched to an alternative treatment prior to conception and before contraception is discontinued (see section 4.3).

In case of pregnancy:

If a woman using NAVALPRO CR becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with NAVALPRO CR and consider alternative options. Patients with a NAVALPRO CR-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.3 and 4.6).

Educational materials:

In order to assist healthcare professionals and patients in avoiding exposure to NAVALPRO CR during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of NAVALPRO CR in women of childbearing potential and includes the details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using NAVALPRO CR (see section 4.3). An Annual Risk Acknowledgement Form needs to be used at the time of treatment initiation and during each annual review of valproate treatment by the medical practitioner.

Male children and men

All male patients should be made aware of the potential risk to children born to men treated with valproate, as in NAVALPRO CR, in the 3 months before conception (see also section 4.6), of the risk of infertility in men (see sections 4.6 and 4.8) and of the data available showing testicular toxicity in animals exposed to valproate and the uncertain clinical relevance.

A retrospective observational study suggests an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, medical practitioners should inform male patients about this potential risk (see section 4.6) and recommend the need for male patients and their female partner to use effective contraception, while using valproate, as in NAVALPRO CR, and for at least 3 months after treatment discontinuation.

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate, as in NAVALPRO CR, should be regularly reviewed by their medical practitioner. For male patients planning to conceive a child, the medical practitioner should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate, as in NAVALPRO CR.

For males aged under 55 years, at initiation of treatment, the medical practitioner should discuss and complete the risk acknowledgement form with the patient at initiation to ensure all male children and men aged under 55 years are aware of the potential risk to offspring and of the risk of infertility in males and testicular toxicity data in animals.

Severe liver damage:

Conditions of occurrence:

Cases of severe liver damage, resulting in fatalities have been reported (see section 4.3).

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular, the following conditions, which may precede jaundice, should be taken into consideration:

- non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy and/or 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 CR.

Patients 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 tests should be performed before therapy is initiated and then periodically monitored during the first 6 months of therapy. Increased liver enzymes may be noted, particularly at the beginning of therapy.

More extensive biological investigation (including prothrombin rate) is recommended in patients developing increased liver enzymes. An adjustment of dosage (decrease) may be needed when appropriate and tests should be repeated as necessary. 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 CR therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued, since they use the same metabolic pathway.

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been reported. This risk is 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. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, NAVALPRO CR should be discontinued.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines, including NAVALPRO CR in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic drugs showed an 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 CR. Patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

Aggravated convulsions:

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 CR.

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

Carbapenem antibiotics:

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

Patients with known or suspected mitochondrial disease:

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

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

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 section 5.2).

Systemic lupus erythematosus:

Although immune disorders have been infrequently noted during the use of NAVALPRO CR, the potential benefit of NAVALPRO CR should be weighed against the risk in patients with systemic lupus erythematosus (see section 4.8). New development and exacerbation of Systemic Lupus Erythematosus (SLE) may occur.

Diabetic patients:

NAVALPRO CR is eliminated mainly through the kidney, partly in the form of ketone bodies, and this may give false-positive readings in the urine testing of possible diabetics.

Hyperammonaemia:

NAVALPRO CR may cause hyperammonaemia.

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

Cases of isolated and moderate hyperammonaemia without change in liver function tests are usually transient and should not lead to treatment discontinuation. However, they may present clinically as vomiting, ataxia, and clouding of consciousness. Should these symptoms occur, NAVALPRO CR should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.

Hypocarnitinemia:

NAVALPRO CR administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonaemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia, when treated with NAVALPRO CR include patients with metabolic disorders, including mitochondrial disorders related to carnitine (see warnings on *Patients with known or suspected mitochondrial*

disease and *Hyperammonaemia*), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics. Patients should be warned to immediately report any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed.

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

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking NAVALPRO CR. Carnitine supplementation should be considered in these patients (see sections 4.3, 4.5 and 4.8).

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

Alcohol:

Alcohol intake is not recommended during treatment with NAVALPRO CR.

Elderly patients (65 years or older):

Elderly patients tend to have increased free, unbound valproate concentrations and lowered intrinsic clearances, indicating a reduction of valproate metabolising capacity and a fall in serum albumin. These patients may also be more susceptible to certain adverse reactions, including

somnolence. Therefore, these patients should receive a lower daily dosage, and the serum concentrations should be kept in the lower therapeutic range.

Dental:

Valproate, as in NAVALPRO CR, inhibits the secondary phase of platelet aggregation, which may be reflected in prolonged bleeding time and/or frank haemorrhaging. In addition, the leukopenic and thrombocytopenic effects of valproate may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work, whenever possible, should be deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss and toothpicks.

Surgical:

Because of the thrombocytopenic effects of valproate, as well as its inhibition of the secondary phase of platelet aggregation and production of abnormal coagulation parameters (e.g., low fibrinogen), monitoring of platelet counts and coagulation tests are recommended in patients prior to scheduled surgery.

Excipients

NAVALPRO CR 200:

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

NAVALPRO CR 300:

This medicinal product contains 27,71 mg sodium per film-coated tablet, equivalent to 1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

NAVALPRO CR 500:

This medicinal product contains 46,16 mg sodium per film-coated tablet, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

Effects of NAVALPRO CR on other medicines

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

NAVALPRO CR may potentiate the effect of other psychotropics medicines such as antipsychotics, MAO inhibitors including linezolid, antidepressants and benzodiazepines. Patients should be monitored, and the dosage should be adjusted when appropriate.

Lithium

NAVALPRO CR has no effect on serum lithium levels.

Olanzapine

NAVALPRO CR may decrease the olanzapine plasma concentration.

Adding olanzapine to valproate, as in NAVALPRO CR, 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 CR and quetiapine may increase the risk of neutropenia/leucopoenia.

Phenobarbital

NAVALPRO CR increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur. Clinical monitoring is recommended right through the first 15 days of combined treatment. Phenobarbital doses should immediately be reduced if sedation occurs, and phenobarbital plasma levels determined when appropriate.

Primidone

NAVALPRO CR increases primidone plasma levels, thereby aggravating its adverse effects (such as sedation). These symptoms usually cease with long-term treatment. Clinical monitoring is recommended, especially at the beginning of combined therapy, with dosage adjustment when appropriate.

Phenytoin

NAVALPRO CR decreases phenytoin total plasma concentration. Moreover, NAVALPRO CR increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Clinical

monitoring is consequently recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

Carbamazepine

NAVALPRO CR, co-administered with carbamazepine may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended, especially at the beginning of combined therapy; dosage adjustment should be applied when appropriate.

Lamotrigine

NAVALPRO CR may reduce lamotrigine metabolism and increase its mean half-life; the lamotrigine dosage should be decreased when appropriate. The risk of rash may possibly be increased by co-administration of lamotrigine with NAVALPRO CR. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes.

Felbamate

NAVALPRO CR may decrease the felbamate mean clearance by up to 16 %.

Rufinamide

NAVALPRO CR may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid, as in NAVALPRO CR. Caution should be exercised.

Propofol

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

Zidovudine

NAVALPRO CR may raise zidovudine plasma concentration, which may result in an increase in zidovudine toxicity.

Nimodipine

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

Effects of other medicines on NAVALPRO CR

By lowering the seizure threshold, antidepressants and neuroleptics may antagonise the antiepileptic activity of NAVALPRO CR and may require NAVALPRO CR dosage adjustments.

Antiepileptics

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to clinical response and blood levels where combined therapy is used.

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

On the other hand, combination of felbamate and NAVALPRO CR decreases valproic acid clearance by 22 % to 50 %, and consequently increases the valproic acid plasma concentrations. NAVALPRO CR dosage should be monitored.

Anti-malarial medicines

Mefloquine increases valproic acid metabolism and may lower the seizure threshold. Chloroquine may also lower the seizure threshold. Accordingly, the dosage of NAVALPRO CR may need adjustment.

High protein bound medicines

During concomitant use of NAVALPRO CR and highly protein bound medicines (aspirin), valproate free serum levels may be increased.

Vitamin K-dependent 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 CR.

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 (such as imipenem, panipenem and meropenem)

Decrease in valproate blood levels, sometimes associated with convulsions, has been observed when it is co-administered with carbapenem antibiotics resulting in a 60 % to 100 % decrease in valproic acid levels within two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem medicines in patients stabilised on valproic acid should be avoided (section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproate blood level is recommended.

Cholestyramine

Cholestyramine may lead to a decrease in plasma levels of NAVALPRO CR when co-administered.

Rifampicin

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

Protease inhibitors

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

Although formal interaction studies have not been performed, available data suggest a reduction ranging from 40 % to 77,5 % in valproate plasma levels.

Patients using protease inhibitors such as ritonavir for the treatment of HIV infection should be carefully monitored for decreased control of their epilepsy/mood status of bipolar patients if also treated with NAVALPRO CR.

Other interactions

Estrogen and progesterone

Estrogens 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.

NAVALPRO CR usually has no enzyme inducing effect; consequently NAVALPRO CR does not reduce the efficacy of ~~o~~estrogen- and/or progestogen- containing medicines in women receiving hormonal contraception.

Topiramate and acetazolamide

Concomitant administration of NAVALPRO CR and topiramate or acetazolamide has been associated with encephalopathy, metabolic acidosis and/or hyperammonaemia. Patients treated with these two medicines should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.

Metamizole

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

4.6 Fertility, pregnancy and lactation

- NAVALPRO CR is contraindicated as treatment for epilepsy during pregnancy, unless there is no suitable alternative treatment (see sections 4.3 and 4.4).
- NAVALPRO CR should not be used in pregnancy for the treatment of bipolar disorder.
- NAVALPRO CR is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.4).

The use of NAVALPRO CR is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential (see above and section 4.3 and 4.4)

Estrogen-containing medicines

Estrogen-containing medicines, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, as in NAVALPRO CR, 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

For the epilepsy indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess the valproate, as in NAVALPRO CR therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is

discontinued. If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision-making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of bipolar disorder must be consulted. Treatment with valproate should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered (see section 4.3).

Pregnancy

Teratogenicity and developmental effects from female and male exposure

Pregnancy exposure risk related to NAVALPRO CR

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

Congenital Malformations

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

Available data show an increased incidence of minor or major malformations. Malformations most frequently encountered are neural tube defects, facial dysmorphism, cleft lip/palate, craniostenosis, cardio-vascular, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. The incidence of neural tube defects in women taking NAVALPRO CR during first trimester has been estimated to be in the region of 1 %.

In utero exposure to NAVALPRO CR may also result in hearing impairment/loss 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 had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

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

Neurodevelopmental disorders from in utero exposure

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

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

Developmental problems have been reported in up to 30 % to 40 % of pre-school children exposed to valproate, as in NAVALPRO CR *in utero*, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

Intelligence quotient (IQ) measured in 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 antiepileptics during pregnancy, although the role of confounding factors cannot be excluded. There is evidence in children exposed to valproate, as in NAVALPRO CR, that the risk of intellectual impairment may be independent from maternal IQ.

There is limited data on the long-term outcomes.

Children exposed to valproate *in utero* are also at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population).

Available data suggesting that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD) (approximately 1,5 times higher than the unexposed population).

NAVALPRO CR as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable treatment (see section 4.3 and 4.4). If a woman using NAVALPRO CR becomes pregnant, she must be immediately referred to a medical practitioner 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 NAVALPRO CR in pregnancy and after careful

consideration of alternative treatment, a pregnant woman must receive NAVALPRO CR for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of NAVALPRO CR 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 NAVALPRO CR-exposed pregnancy and their partners should be referred to a medical practitioner 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, as in NAVALPRO CR exposure.

Other risks in the neonate

- Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken NAVALPRO CR during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to decreases in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome has to be distinguished from the decrease of the vitamin K factors induced by phenobarbital and other antiepileptic enzyme inducing medicines. 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 CR during the third trimester of the pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate, as in NAVALPRO CR, during the last trimester of their pregnancy.
- Hepatic failure, resulting in the death of a newborn and of an infant have been reported following the use of valproate during pregnancy.

Breastfeeding

Valproate is distributed into breast milk. Concentrations in breast milk have been reported to be 1 % to 10 % of the total maternal serum concentrations (see section 4.3).

Mothers on NAVALPRO CR should not breastfeed their infants (see section 4.3).

Cases of haematological changes and somnolence have been reported in infants of mothers taking NAVALPRO CR, when breastfeeding their infants.

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

Fertility

Amenorrhoea, menstrual disorders, polycystic ovaries, increased testosterone levels, and impairment of ovarian function and of fertility have been reported in female patients using NAVALPRO CR (see section 4.8.).

Valproate, as in NAVALPRO CR, may also impair fertility in men (see sections 4.4 and 4.8). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

Males and potential risk of neurodevelopmental disorders in children of fathers treated with valproate, as in NAVALPRO CR, in the 3 months prior to conception.

A retrospective observational study in 3 Nordic countries suggests an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, medical practitioners should inform male patients about this potential risk and recommend the need for male patients and their female partner to use effective contraception, while using valproate, as in NAVALPRO CR, and for at least 3 months after treatment discontinuation (see section 4.4).

Male patients should not donate sperm during treatment or for at least 3 months after treatment discontinuation.

Male patients treated with valproate, as in NAVALPRO CR, should be regularly reviewed by their medical practitioner. For male patients planning to conceive a child, the medical practitioner should consider and discuss other suitable treatment options with the male patients. Individual circumstances should be evaluated in each case.

4.7 Effects on ability to drive and use machines

NAVALPRO CR has moderate influence on the on the ability to drive or operate machinery. Since adverse effects such as somnolence, dizziness and visual disturbances have been reported in patients receiving NAVALPRO CR, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that NAVALPRO CR does not affect their ability to do so (see section 4.8.). Patients should be warned of the risk of cases of anticonvulsant polytherapy with NAVALPRO CR or concomitant treatment with benzodiazepine (see section 4.5).

4.8 Undesirable effects

a) Tabulated summary of adverse events

The following side effects have been observed during treatment with NAVALPRO CR:

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	Anaemia, thrombocytopenia (see section 4.4)	Platelet aggregation inhibition, reversible prolongation of bleeding time, bone marrow failure, red cell hyperplasia, leucopoenia, isolated reduction of fibrinogen, pancytopenia, agranulocytosis, anaemia macrocytic, macrocytosis	
Immune system disorders		Allergic reactions	
Endocrine disorders		Hyperglycaemia, syndrome of inappropriate secretion of ADH (SIADH), hypothyroidism. hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or increased androgen)	
Metabolism and nutrition disorders	Hyponatraemia, increased weight	Hyperammonaemia, obesity	Hyperammonaemic encephalopathy in patients with urea cycle disorders, hyperglycinaemia.

Psychiatric disorders	Amnesia, sleep disorders, primarily insomnia, nervousness, somnolence, drowsiness, emotional lability, confusional state, aggression, disturbance in attention	Behavioural, mood or mental changes, abnormal dreams, agitation, anxiety, confusion, depression, hallucinations, thinking abnormalities, unusual excitement, restlessness, irritability, sedation, psychomotor hyperactivity, learning disorder	
Nervous system disorders	Ataxia, extrapyramidal disorder, stupor, convulsion, memory impairment, tremor, headache, nystagmus, dizziness.	Abnormal gait, encephalopathy, lethargy, reversible parkinsonism, coma, catatonic reaction, dysarthria, hypertonia, hypokinesia, paraesthesia, increased reflexes, speech disorder, tardive dyskinesia, twitching, increased alertness, reversible dementia associated with cerebral atrophy, aggravated convulsions, cognitive disorder	
Eye disorders	Amblyopia	Spots before eyes, diplopia, conjunctivitis, dry eyes, eye pain	
Ear and labyrinth disorders	Tinnitus, deafness	Otitis media, vertigo, ear disorder or pain	
Cardiac disorders		Palpitations, tachycardia	
Vascular disorders	Haemorrhage	Hypotension, hypertension, postural hypotension, vasodilation, vasculitis	
Respiratory, thoracic and mediastinal disorders	Pharyngitis, flu syndrome	Dyspnoea, pneumonia, bronchitis, epistaxis, increased cough, rhinitis, sinusitis, pleural effusion	
Gastrointestinal disorders	Abdominal or stomach cramps, diarrhoea, dyspepsia, nausea and vomiting, indigestion, gingival disorder (mainly gingival hyperplasia) stomatitis	Hematemesis, periodontal abscess, anorexia or increase in appetite, constipation, dry mouth, faecal incontinence, flatulence, gastroenteritis, glossitis, taste perversion, minor gastric irritation, life threatening pancreatitis	
Hepatobiliary disorders	Liver injury		Liver dysfunction, hepatic failure, fatal hepatoxicity
Skin and subcutaneous tissue disorders	Alopecia, skin rash, nail and nail bed disorders, hypersensitivity	Angioedema, Discoid lupus erythematosus, dry skin, ecchymosis, furunculosis, petechia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme,	

		Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)	
Musculoskeletal and connective tissue disorders	Back pain	Leg cramps, malaise, neck pain, neck rigidity, arthralgia, arthrosis, hypertonia, myalgia, myasthenia, bone mineral density decreased, osteopenia, osteoporosis, fractures in patients on long-term treatment, development and worsening of systemic lupus erythematosus, rhabdomyolysis	
Renal and urinary disorders	Urinary incontinence	Renal failure, tubulointerstitial nephritis, cystitis, dysuria, reversible defects in renal tubular function (Fanconi's syndrome-glycosuria, amino aciduria, phosphaturia, and uricosuria), enuresis	
Reproductive system and breast disorders	Change in menstrual periods, dysmenorrhoea,	Vaginal haemorrhage, amenorrhoea, metrorrhagia, vaginitis, gynaecomastia, male infertility, polycystic ovaries, impairment of ovarian function and of fertility in females	
Congenital and familial and genetic disorders			See "Congenital Malformations" "Teratogenicity" and "Developmental effects (section 4.6)
General disorders and administrative site conditions	Infections, asthenia	Peripheral oedema (swelling), fatigue, unusual weight gain or loss, fever, chest pain, chills, oedema, malaise, hypothermia	
Investigations		Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR increased biotin deficiency/ biotinidase deficiency).	Diagnostic tests: Metyrapone test: decreased response to metyrapone. Thyroid function test: decreased T_4 and free T_3 and T_4 concentrations. Urine ketone test: false-positive results. Physiology/laboratory test values Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) and Lactate dehydrogenase (LDH): minor elevations of serum concentrations occur frequently and appear to be dose related; elevations may

			indicate asymptomatic hepatotoxicity. Amino acid screening increases in glycine may occur. Bilirubin: serum concentrations may be increased; increase may indicate potentially serious hepatotoxicity

b) Description of selected adverse reaction

Blood and lymphatic system disorders

The haematological profile returned to normal when NAVALPRO CR 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 CR has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of NAVALPRO CR pending investigations (see section 4.4).

Nervous system disorders

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

Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely

been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

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

Children exposed *in utero*: Neurodevelopmental problems such as late walking and talking, poor language skills, memory problems, lower intellectual abilities, autistic syndrome and ADHD have been observed in children exposed *in utero* (see section 4.6)

Endocrine disorder

Plasma amylase should be measured if there is acute abdominal pain.

Gastrointestinal disorders

Common gastrointestinal adverse events, such as nausea and vomiting, frequently occur at the start of treatment, but usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking NAVALPRO CR with or after food.

Hepatobiliary disorders

Hepatic failure resulting in death has occurred in patients taking NAVALPRO CR. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, vomiting, jaundice and oedema (see section 4.3 and 4.4).

Increased liver enzymes are common, particularly early in treatment, and may be transient.

Skin and subcutaneous tissue disorders

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

Musculoskeletal and connective tissue disorders

There is a higher risk of osteoporosis and fractures in patients on long-term therapy with NAVALPRO CR. Risk factors include a history of osteoporosis and concomitant steroid use.

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** via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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.

Signs of acute massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, may include CNS depression, coma with muscular hypotonia, hyporeflexia,

miosis, metabolic acidosis, hypotension, circulatory collapse/shock and respiration may be impaired. Full recovery is usual following treatment.

Deaths have occurred following massive overdose.

Seizures have been reported in the presence of very high plasma levels of valproate, as in NAVALPRO CR (see section 4.8). Cases of intracranial hypertension related to cerebral oedema have been reported.

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

Treatment

Treatment of overdose consists primarily of supportive and symptomatic measures.

Administration of activated charcoal may be useful following ingestion.

Cardiorespiratory monitoring assisted ventilation and other supportive measures are recommended.

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

In case of NAVALPRO CR overdose resulting in hyperammonaemia, carnitine can be given through IV route to attempt to normalise ammonia levels.

Naloxone has been used in a few cases.

To decrease absorption – The effectiveness of emesis will depend upon the time elapsed since ingestion.

To enhance elimination – Haemodialysis, or tandem haemodialysis and haemoperfusion, may result in significant reductions in valproate serum concentrations.

Specific treatment – Maintenance of adequate urinary output must be ensured. Naloxone has been administered to counteract severe CNS depression, but it also theoretically reverses the anticonvulsant effect and should be used with caution.

Supportive care – Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including antiepileptics

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 a potentiation of the inhibitory action of gamma-amino butyric acid (GABA) in the brain 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 between 30 and 100 µg/mℓ. This range may depend on time of sampling and presence of co-medicatioine. The percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels.

The pharmacological (or therapeutic) effects of sodium valproate 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

Valproate is absorbed rapidly and completely after oral administration.

Peak plasma concentration is observed in 1 to 4 hours, although this can be delayed for several hours if given with food, if valproate is administered in enteric-coated tablets, or in prolonged release formulation.

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

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

Valproate is highly bound to plasma proteins; the apparent volume of distribution is about 0,2 litre/kg. Protein binding is dose dependent and saturable. Its extent of binding to plasma proteins is usually about 90 %, but the fraction bound is reduced as the total concentration of valproate is increased through the therapeutic range.

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

Placental transfer: valproate crosses the placental barrier in animal species and in humans:

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

Biotransformation

Valproate (95 %) undergoes hepatic metabolism, with less than 5 % excreted unchanged in urine. Its hepatic metabolism occurs mainly by UGT enzymes and ß-oxidation.

Valproate is a substrate for CYP2C9 and CYP2C19, but metabolism by these enzymes accounts for a relatively minor portion of its elimination. 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 medicine metabolites, notably 2-propyl-2-pentenoic acid and 2-propyl-4-pentenoic acid, are nearly as potent antiseizure medicines as the parent compound; however, only the former (2-en-valproic acid) accumulates in plasma and brain to a potentially significant extent.

Elimination

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

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

The half-life of valproate is approximately ~~15~~ 8 to 20 hours but is reduced in patients taking other antiepileptic medicines.

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

Acesulfame potassium, basic butylated methacrylate copolymer, colloidal hydrate silica, dibutyl sebacate, hypromellose, magnesium stearate, sodium lauryl sulphate, titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

NAVALPRO CR 200: 24 months.

NAVALPRO CR 300: 36 months.

NAVALPRO CR 500: 36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton in order to protect from light and moisture.

6.5 Nature and contents of container

NAVALPRO CR tablets are packed in packs of 56 or 100 tablets in blisters made of silver oPA/Al/PVC foil and Aluminium push-through foil. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATES OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

0800 122 912

8. REGISTRATION NUMBERS

NAVALPRO CR 200: 45/2.5/0411

NAVALPRO CR 300: 45/2.5/0091

NAVALPRO CR 500: 45/2.5/0092

9. DATE OF FIRST AUTHORISATION

01 March 2013

10. DATE OF REVISION OF TEXT

31 July 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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