1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

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

COMPOSITION

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

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

Sugar free

CATEGORY AND CLASS

A 2.5 Anticonvulsants including anti-epileptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

Pharmacokinetic properties

Peak plasma concentration is reached at the end of a 1-hour intravenous infusion. The half-life is variable but is approximately 16 hours after intravenous infusion of 1 000 mg over 1 hour.

Protein binding is usually high (90 to 95 %) but decreases as the serum concentration increases. It is also decreased in the elderly, in patients with chronic hepatic diseases and in renal impairment. Sodium valproate is distributed in the cerebrospinal fluid and the concentration is similar to that of the unbound concentration in plasma. It is also distributed into breast milk (1 to 10 % of maternal serum concentrations). The reported effective therapeutic range for plasma valproic acid levels in epilepsy is considered to be between 30 and 100 µg/ml. Sodium valproate is primarily metabolised in the liver, with some of the metabolites being active. It is renally excreted mainly as the glucuronide conjugate.

INDICATIONS

NAVALPRO 400 mg/4 ml is indicated for the short-term therapy of grand mal, petit mal, mixed generalised epilepsy and temporal lobe (psychomotor) epilepsy, when oral treatment is not possible.

CONTRAINDICATIONS

- Hypersensitivity to NAVALPRO 400 mg/4 ml or to any components of the formulation.
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- Active liver disease, including the following:
    - Acute hepatitis.
    - Chronic hepatitis.
    - Personal or family history of hepatic dysfunction especially medicine related.
    - Porphyria.

NAVALPRO 400 mg/4 ml has been shown to be porphyrinogenic in animals or *in vitro* systems. Use of NAVALPRO 400 mg/4 ml may result in an acute attack.

WARNINGS AND SPECIAL PRECAUTIONS

Use with caution in patients with:

- Pancreatitis. Discontinue NAVALPRO 400 mg/4 ml if patient develops pancreatitis as it may be life-threatening. 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 (see SIDE EFFECTS).
- Systemic lupus erythematosus.
- Renal impairment, as serum levels may increase, resulting in toxicity.
- Blood dyscrasias. Monitor bleeding time and blood cell counts, especially before surgery.
- Hypoalbuminaemia, as serum levels of NAVALPRO 400 mg/4 ml may increase.

Liver dysfunction, which may result in death, has occurred in patients receiving NAVALPRO 400 mg/4 ml. This usually occurs within the first few months of therapy and children under the age of three years who are taking other anticonvulsants are at highest risk. Any signs of hepatotoxicity (asthenia, drowsiness, lethargy, jaundice, abdominal pain, vomiting, weakness, anorexia) should be reported to the medical practitioner immediately (see SIDE EFFECTS). Liver function tests should be carried out before therapy (see CONTRAINDICATIONS), and periodically during the first 6 months especially in patients at risk.
Mild increased liver enzymes may be noted, particularly at the beginning of therapy.

More extensive biological investigations (including INR) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.
The concomitant use of salicylates should be avoided in those children under 3 years of age due to the risk of liver toxicity.

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

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

Confusion; cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; they may be associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbital) or after a sudden increase in valproate doses. Cases of reversible dementia associated with cerebral atrophy have been reported. Reversible Parkinsonism has been reported. Transient and (or) dose related fine postural tremor and somnolence have often been reported.

Effects on ability to drive and use machines

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

INTERACTIONS

Concomitant use of NAVALPRO 400 mg/4 ml with:

Anticoagulants and thrombolytic medicines may increase the risk of haemorrhage. In case of concomitant use of NAVALPRO 400 mg/4 ml and highly protein bound medicines (aspirin), valproate free serum levels may be increased.

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 400 mg/4 ml.

Clonazepam may produce absence status epilepticus in patients with a history of absence type seizures.

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

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

Phenytoin:

NAVALPRO 400 mg/4 ml decreases phenytoin total plasma concentration. Moreover NAVALPRO 400 mg/4 ml 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 400 mg/4 ml was administered with carbamazepine as valproate may potentiate toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Carbamazepine and phenytoin are enzyme inducers and therefore decrease serum levels of NAVALPRO 400 mg/4 ml.

Lamotrigine metabolism is inhibited by NAVALPRO 400 mg/4 ml and this may result in serious toxic dermatological reactions.

Phenobarbital:

NAVALPRO 400 mg/4 ml increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

Primidone:

NAVALPRO 400 mg/4 ml increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

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

Mefloquine and chloroquine, lowers the seizure threshold and reduces the serum concentration of NAVALPRO 400 mg/4 ml.

Zidovudine:

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

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

Carbapenem antibiotics (imipenem/meropenem/ertapenem): 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.

NAVALPRO 400 mg/4 ml does not reduce efficacy of oestrogen and/or progestogen containing medicines in women receiving hormonal contraception.

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

HUMAN REPRODUCTION

Pregnancy

NAVALPRO 400 mg/4 ml is contraindicated during pregnancy. Neural tube defects have been reported following exposure during the first trimester.

From experience in treated epileptic mothers, the risk associated with the use of NAVALPRO 400 mg/4 ml during pregnancy has been described as follows:

Risk associated with epilepsy and anti-epileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in case of multiple medicine therapy, the respective part of treatments and disease has not been formally established. Malformations most frequently

encountered are labial clefts and cardiovascular malformations.

Developmental delay has been reported in children born to mothers with epilepsy.

It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both the mother and the fetus.

Risk associated with sodium valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

Pregnant women should not use NAVALPRO 400 mg/4 ml.

Risk in the neonate

Cases of haemorrhagic syndrome have been reported in neonates whose mothers have used NAVALPRO 400 mg/4 ml during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia; afibrinogenaemia has also been reported and may be fatal. Hypofibrinogenaemia is possibly associated with decrease of coagulation factors.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation

NAVALPRO 400 mg/4 ml is contraindicated in breastfeeding mothers. When given to breastfeeding mothers, NAVALPRO 400 mg/4 ml is excreted in breast milk. Concentrations of

NAVALPRO 400 mg/4 ml in breast milk have been found to be 1 to 10 % of total maternal serum concentration.

DOSAGE AND DIRECTIONS FOR USE

- **Dose in adults and adolescents**

  Replacement for oral therapy:

  Patients should continue on their current daily dose using continuous or repeated infusion, administered at the same frequency as the oral dose. If the total daily dose exceeds 250 mg, it should be given in divided doses.

  Initial exposure to NAVALPRO 400 mg/4 ml:

  400 mg to 800 mg depending on body mass (up to 10 mg/kg) by slow intravenous injection over 3 to 5 minutes, usually followed by continuous or repeated infusion up to a maximum of 2500 mg/day, or one other anti-epileptic medicine may be added at a low dosage.

  Combination therapy:

  It may be necessary to increase the dose by 5 to 10 mg/kg/day when NAVALPRO 400 mg/4 ml is used with other anticonvulsants which induce liver enzymes. Dosage may have to be reduced when the other medicine is withdrawn. In patients already receiving other therapy, the same pattern should be followed. If increased sedation is observed, dosage of barbiturates should be reduced as that of NAVALPRO 400 mg/4 ml is increased. Dosage of both NAVALPRO 400 mg/4 ml and other medicines should be adjusted during the stabilization period to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with NAVALPRO 400 mg/4 ml alone.

- **Children dose (≥ 20 kg)**

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

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

- **Children dose < 20 kg:**

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

- **Elderly**

  The pharmacokinetics of NAVALPRO 400 mg/4 ml is altered in the elderly, resulting in higher concentrations of free valproate. The dosage may need to be reduced in the elderly.

- **Patients with 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 PHARMACOKINETIC PROPERTIES).

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

The concentration of NAVALPRO 400 mg/4 ml in plasma that appears to be associated with therapeutic effects is approximately 40 to 100 µg/ml. A method of measuring plasma levels is available. Therapeutic NAVALPRO 400 mg/4 ml plasma levels do not imply optimal seizure control; therefore, the optimal NAVALPRO 400 mg/4 ml dosage for a particular patient is mainly

determined by seizure control. NAVALPRO 400 mg/4 ml plasma levels may however be helpful where there is poor seizure control or when side effects are suspected.

To reconstitute NAVALPRO 400 mg/4 ml, add the solvent provided (4 ml of Water for Injection) to the vial, allow it to dissolve and extract the appropriate dose. Due to displacement of solvent by sodium valproate the concentration of reconstituted sodium valproate is 95 mg/ml.
NAVALPRO 400 mg/4 ml may be given either by direct slow intravenous injection or by infusion in normal saline, dextrose saline or dextrose 5 %, using a separate intravenous line. It should not be administered via the same IV line as other IV additives.

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

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

SIDE EFFECTS

Blood and lymphatic system disorders

Frequent: Thrombocytopenia

Less frequent: Reversible prolongation of bleeding time, leucopenia or pancytopenia and bone marrow depression. Monitor platelet function before major surgery

Immune system disorders

Less frequent: Systemic lupus erythematosus, allergic reactions, rashes (toxic epidermal necrolysis, Stevens-Johnson syndrome or erythema multiforme)

Metabolism and nutritional disorders

Frequent: Weight gain

Less frequent: Hyperammonaemia, even in the absence of hepatic impairment. May be associated with neurological symptoms

Psychiatric disorders

Less frequent: Hallucinations, stupor, coma, confusion, aggression, hyperactivity, behavioural disturbances and reversible dementia associated with cerebral atrophy

Nervous system disorders

Less frequent: Sedation, ataxia, tremor, lethargy and extrapyramidal symptoms; encephalopathy and coma

Frequency unknown: Dizziness

Ear and labyrinth disorders

Less frequent: Hearing loss, either reversible or irreversible

Vascular disorders

Less frequent: Oedema, vasculitis

Gastrointestinal disorders

Frequent: Increased appetite, nausea, gastralgia, diarrhoea, vomiting, constipation

Less frequent: Pancreatitis, polydipsia

Hepato-biliary disorders

Frequent: Transient elevation of liver enzymes (15 to 30 % of patients)

Less frequent: Liver dysfunction, including hepatic failure. This usually occurs within the first few

months of treatment and in children under the age of three years receiving other anticonvulsants. Discontinue therapy with NAVALPRO 400 mg/4 ml (see WARNINGS AND SPECIAL PRECAUTIONS)

Skin and subcutaneous tissue disorders

Less frequent: Transient hair loss with regrowth of curly hair (not likely with short-term use), hirsutism, acne, diaphoresis

Reproductive system and breast disorders

Less frequent: Irregular periods, amenorrhoea, gynaecomastia

Renal and urinary disorders

Less frequent: Fanconi's syndrome (a defect in proximal renal tubular function), polyuria, enuresis

General disorders and administrative site conditions

Frequency unknown: Inflammatory reactions and pain at the site of injection

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

Symptoms

At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, the only likely symptoms are nausea, vomiting and dizziness. Clinical signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis and impaired respiratory function. Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

Treatment

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

Naloxone has been successfully used in a few isolated cases.

Deaths have occurred following massive overdose.

IDENTIFICATION

Vial: A white lyophilised powder.

Ampoule: A transparent and colourless liquid.

Reconstituted solution: A clear, colourless solution.

PRESENTATION

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

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

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

STORAGE INSTRUCTIONS

Store at or below 25 °C.

From a microbiological point of view, the solutions must be used immediately after

reconstitution, and other conditions of use are the responsibility of the user and should not be more than 24 hours in a fridge, unless controlled and validated aseptic conditions are applied.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A40/2.5/0342

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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