

HOVID VALPROATE LIQUID 200MG / 5ML

DESCRIPTION

A red, cherry flavoured liquid.

COMPOSITION

Each 5 ml contains Sodium Valproate 200 mg.

PHARMACODYNAMICS

Sodium valproate is an anticonvulsant.

The most likely mode of action for Hovid Valproate Liquid is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

PHARMACOKINETICS

The half-life of Hovid Valproate Liquid is usually reported to be within the range 8-20 hours. It is usually shorter in children.

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

The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of comedication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Hovid Valproate Liquid may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

NONCLINICAL SAFETY DATA

Reproductive and developmental toxicity

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits.

In published literature, behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice, behavioural changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation. The relevance of these findings for humans is unknown.

Impairment of fertility

In sub-chronic / chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Relevance of the testicular findings to pediatric population is unknown.

INDICATION

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

- Absence
- Myoclonic
- tonic-clonic
- atonic
- mixed

As well as, for partial epilepsy:

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

Treatment and prevention of mania associated with bipolar disorder.

CONTRAINDICATIONS

- Active liver disease
- History of severe hepatic dysfunction
- Hypersensitivity to sodium valproate
- Porphyria

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

- In epilepsy
 - Sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
 - Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)
- In bipolar disorder
 - Sodium valproate is contraindicated in pregnancy
 - Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)

WARNINGS AND PRECAUTIONS

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

Use in male patients of reproductive potential: A retrospective observational study indicates 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 treated with lamotrigine or levamisole (see Pregnancy and Lactation). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counselling in case of pregnancy if he used valproate within 3 months prior to conception.

The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to all men of reproductive potential using valproate.

Liver dysfunction: Conditions of occurrence: Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation.

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

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years.

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

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

Suggestive signs: Clinical symptoms are essential for early

diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk:

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

These are an indication for immediate withdrawal of the drug.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately.

Detection: Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin and raised transaminases) requires cessation of Hovid Valproate 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.

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

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

PANCREATITIS: CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA MAY BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

Female children, Women of childbearing potential, and pregnant women:

Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In pregnancy for bipolar disorder indication.
- In women of childbearing potential unless below conditions are fulfilled.

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 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 sodium valproate in utero.
 - The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception. If possible (see Fertility, Pregnancy and Lactation). Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy.

- 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 sodium valproate.
- The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to discuss the need for discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with sodium 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 doctor once the female child using sodium valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with sodium valproate. Pregnancy must be excluded before initiation 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 sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium 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 ensure understanding of the risks and measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by the prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber 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 prescriber experienced in the management of epilepsy must reassess sodium 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. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber, at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

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

Potential for an increase in risk of suicidal thoughts and behaviours: Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications.

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

Carbapenem agents: The concomitant use of valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:

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

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal or generalized), 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.

Haematological: 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 Adverse effects).

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.

Systemic lupus erythematosus: Although immune disorders have only rarely been noted during the use of Hovid Valproate Liquid, the potential benefit of Hovid Valproate Liquid should be weighed against its potential risk in patients with systemic lupus erythematosus (See Adverse effects).

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

Weight gain: Hovid Valproate Liquid very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it (See Adverse effects).

Diabetic patients: Hovid Valproate Liquid is eliminated mainly through the kidneys, partly in the form of ketone bodies. It may give false positives in the urine testing of possible diabetics.

In addition, care should be taken when treating diabetic patients with Hovid Valproate Liquid since it contains sucrose.

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 Hovid Valproate Liquid.

Alcohol: Alcohol intake is not recommended during treatment with valproate

PREGNANCY AND LACTATION

Fertility, Pregnancy and Lactation:

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.
- Sodium valproate is contraindicated for use in women of childbearing potential, unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections)

Pregnancy Exposure Risk related to sodium valproate

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

Teratogenicity and developmental effects

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 sodium valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. 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 sodium valproate 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 sodium valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of sodium valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to sodium 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 sodium valproate in utero are at increased risk of autistic spectrum disorder

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

Female children and woman of childbearing potential (see Contraindications and Warnings and precautions sections).

Risk to children of fathers treated with valproate

A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07).

Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see Warnings and Precautions).

If a woman plans a pregnancy

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium 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. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor 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 sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:

- Use the lowest effective dose and divide the daily dose sodium 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 to avoid high peak plasma concentrations.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor 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 sodium valproate exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors.
- Atrioventricular septal defects have also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding

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

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

Fertility

Valproate administration may also impair fertility in men (see Section Main Side/Adverse Reactions). In the few cases in which valproate was switched / discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed.

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women taking valproate (see Undesirable effects). Valproate administration may also impair fertility in men (see Undesirable effects). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

DRUG INTERACTIONS

Effects of Hovid Valproate Liquid on other drugs

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines: Hovid Valproate Liquid may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is recommended especially at the beginning of psychotropics should be adjusted when appropriate.

Lithium: Hovid Valproate Liquid has no effect on serum lithium levels.

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

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

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

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

Zidovudine: Hovid Valproate Liquid may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

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

Temozolomide: Co-administration of temozolomide and Hovid-Valproate Liquid may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Nimodipine: In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

Effects of other drugs on Hovid Valproate Liquid Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

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

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

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

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

Carbamepem antibiotics such as imipenem, panipenem and meropenem: Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Colestyramine may decrease the absorption of Hovid Valproate Liquid.

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

Other Interactions

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

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

Hovid Valproate Liquid usually has no enzyme-inducing effect; as a consequence, Hovid Valproate Liquid does not reduce efficacy of coestrogenopreventative agents in women receiving hormonal contraception, including the oral contraceptive pill.

Outelapine: Co-administration of Hovid Valproate Liquid and quetiapine may increase the risk of neutropenia/leucopenia.

MAIN SIDE/ADVERSE EFFECTS

Congenital malformations and developmental disorders (see Pregnancy and Lactation)

Hepato-biliary disorders

Common: Liver injury
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient.

Gastrointestinal disorders

Very common: Nausea
Common: Gastralgia, diarrhoea
The above three adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment.

Uncommon: Pancreatitis, sometimes lethal

Nervous system disorders

Very common: Tremor
Common: Extrapyramidal disorder, stupor*, somnolence, decreased memory impairment, headache, nystagmus
Uncommon: Coma*, encephalopathy, lethargy*, reversible parkinsonism, ataxia, paresthesia

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

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 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 anticonvulsants, notably phenobarbital or topiramate.

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

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

Psychiatric disorder

Rare: Confusional state, aggression*, agitation*, disturbance in attention*
Rare: Abnormal behaviour*, psychomotor hyperactivity*, aggression*
*These ADRs are principally observed in the paediatric population.

Metabolic disorders

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

Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.

Endocrine Disorders

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH)
Rare: Hypothyroidism

Blood and lymphatic system disorders

Common: Anaemia, thrombocytopenia
Uncommon: Pancytopenia, leucopenia
The blood picture returned to normal when the drug was discontinued.
Rare: Bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

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 of Hovid Valproate Liquid has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.

Skin and subcutaneous tissue disorders

Common: Hypersensitivity, transient and or dose related alopecia (hair loss). Regrowth normally begins within six months, although the hair may become more curly than previously.
Uncommon: Angioedema, rash
Hirsutism and acne have been very rarely reported.
Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders

Common: Dysmenorrhoea
Uncommon: Amenorrhoea
Rare: Male infertility, polycystic ovaries
Very rarely gynaecomastia has occurred.

Vascular disorders

Common: Haemorrhage
Uncommon: Vasculitis

Ear and labyrinth disorders

Common: Deafness, a cause and effect relationship has not been established

Renal and urinary disorders

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

General disorders and administration site conditions

Uncommon: Non-severe oedema peripheral

Musculoskeletal and connective tissue disorders

Uncommon: Bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Hovid Valproate Liquid. The mechanism by which Hovid Valproate Liquid affects bone metabolism has not been identified.
Rare: Systemic lupus erythematosus

Respiratory, thoracic and mediastinal disorders

Uncommon: Pleural effusion

Investigations

Common: Weight increased*
Rare: Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome

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

OVERDOSE AND TREATMENT

Cases of accidental and deliberate Hovid Valproate Liquid overdose have been reported. 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 massive overdose, i.e. plasma concentration 10 to 20 times maximum therapeutic levels, include: hypotension, depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. The overall outcome is usual; however some deaths have occurred following massive overdose.

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

The presence of sodium content in the sodium valproate syrup formulation may lead to hyponatraemia when taken in overdose.

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

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally. In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

DOSAGE AND ADMINISTRATION

Oral administration.

Daily dosage requirements vary according to age and body weight.

Hovid Valproate Liquid may be given twice daily. Hovid Valproate Liquid should not be diluted.

Usual requirements are as follows:

Adults: Initially 600 mg/day, dose may be increased by 200 mg at 3-day intervals to max 2500 mg/day. Usual maintenance dose: 1000-2000 mg/day (20-30 mg/kg/day).

Children over 20kg: Initially 400 mg/day with spaced increases until control is achieved (usually 20-30 mg/kg/day); dose may be increased to 35 mg/kg/day.

Children under 20kg: 20 mg/kg/day; in severe cases the dose may be increased provided plasma valproic acid levels can be monitored. In children requiring doses above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

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

In patients with renal insufficiency: It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

In patients with hepatic insufficiency: Salicylates should not be used concomitantly with hovid-Valproate Liquid since they employ the same metabolic pathway.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid.

Salicylates should not be used in children under 16 years. In addition in conjunction with hovid-Valproate Liquid, concomitant use in children under 3 years can increase the risk of liver toxicity.

Female children, female adolescents, women of childbearing potential and pregnant women: Hovid Valproate Liquid should be initiated and supervised by a specialist experienced in the management of epilepsy. Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Combined Therapy: When starting Hovid Valproate Liquid in patients already on other anticonvulsants, these should be tapered slowly: initiation of Hovid Valproate Liquid therapy should then be gradual, with target dose being reached after 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10mg/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 it may be possible to maintain seizure control on a reduced dose. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

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

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

Mania associated with bipolar disorder: Adults: The recommended initial dose is 1000mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effects. The recommended maintenance dosage for treatment of bipolar disorder is between 1000mg and 2000mg daily. In exceptional cases, the dose may be increased to not more than 3000mg daily. Doses should be adjusted according to individual clinical response. Prophylactic treatment should be established individually with the lowest effective dose.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C.

Presentation / Packing:
Liquid 200mg / 5mL x amber, round glass bottle of 300 mL
Liquid 200mg / 5mL x amber, plastic bottle of 100 mL and 300 mL

Product Registration Holder (Malaysia) /
Manufactured by: Hovid Berhad,
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar),
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