

DUVALEP

Tablets & Syrup

Composition

Duvallep Tablets

Each enteric-coated tablet contains:

Sodium valproate 200 mg

Duvallep Syrup/Duvallep Sugar-Free syrup

Each teaspoonful (5 ml) contains:

Sodium valproate 200 mg

Action

Duvallep is an anticonvulsant agent, chemically unrelated to other drugs indicated for the treatment of seizure disorders.

The mechanism by which Duvallep exerts its anticonvulsant effects has not yet been established, but it probably increases brain levels of γ -aminobutyric acid (GABA).

Duvallep is rapidly absorbed and distributed after oral administration. The peak blood levels for the liquid form are achieved 1-1.5 hours after intake. For the enteric-coated form, peak blood levels are achieved generally within 2-8 hours, depending on the time of the day, particularly in relation to ingestion of food. The average half-life of sodium valproate at steady state is 12 hours in children and adults. The drug is highly bound (90%) to human plasma proteins. Elimination occurs mainly via the kidney

Indications

Generalized or Partial Epilepsy

Primary generalized epilepsy (including photosensitive forms), preferably as single-drug therapy, in particular: grand mal (with or without myoclonia), petit mal (in this type of epilepsy, valproates also provide protection against the possible occurrence of tonicclonic seizures), juvenile myoclonic epilepsy, grand mal petit mal combination.

Secondary generalized epilepsy, in particular: West syndrome, Lennox-Gestaut syndrome.

Partial epilepsy with elementary symptomatology or with complex symptomatology (such as psychosensory, psychomotor forms), in particular: partial epilepsy with partial seizures secondarily generalized, benign partial epilepsy (with Rolandic or occipital spikes) –elective indication for single-drug therapy.

Mixed Forms

Generalized and partial.

Contraindications

- Known hypersensitivity to the drug.
- Hepatic disease or significant hepatic dysfunction. Personal or family history of severe hepatitis, especially drug-related.

Warnings

Hepatic failure, resulting in fatalities, has occurred in patients receiving valproates, usually during the first 6 months of treatment especially those on multiple anti-convulsant. Infants or young children showing severe epilepsy with mental retardation, cerebral lesions and/or metabolic or degenerative diseases, notably genetic, seem to be more likely to develop such disorders, when Duvallep is used in this patient group, it should be used with extreme caution and a sole agent. In most of the cases of hepatitis, one or more other anticonvulsant drugs were administered concomitantly. However, a

period of greater risk seems to occur between weeks 3-12 of valproate therapy. In some cases, the hepatic disorders become worse, irrespective of valproate withdrawal

In cases of hepatitis, liver function tests have not always been significantly disturbed early in the course of valproate therapy. However, as with other anticonvulsant drugs, transient and/or reversible increases in liver enzymes (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), serum alkaline phosphatase) may be noted in patients on valproate therapy, particularly during the early course of treatment. These increases are often dose-related and unaccompanied by clinical signs or significant changes in serum bilirubin, albumin, fibrinogen, coagulation factors or other liver function tests. If other biological signs of liver dysfunction, such as definite elevations of serum bilirubin or decreases in serum fibrinogen, are observed concurrently with increases in liver enzymes, it is recommended to discontinue valproates immediately. Furthermore, the occurrence, especially after an initial phase of good results on valproates, of signs, even unspecific, such as asthenia, drowsiness, apathy, anorexia, or deterioration of the general condition, possibly accompanied by vomiting and loss of control of epileptic seizures, should be a warning to the physician that liver dysfunction may have developed. In such cases, liver function tests should be performed without delay.

Repeated liver function tests, especially those including serum albumin, fibrinogen, bilirubin and transaminase measurements, should be performed prior to initiation of therapy and at periodic intervals thereafter (particularly during the first 6 months of treatment, and in patients receiving doses higher than 35 mg/kg body weight/day). If the laboratory tests reflect a definite impairment of liver function, it is recommended that valproate therapy be discontinued immediately. Loss of control of seizures, malaise, weakness and edema are indications for immediate withdrawal of the drug

Pregnancy

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers

Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this may have on a nursing infant. Therefore, caution should be exercised when administering this drug to nursing mothers.

Use in Male Patients

Chronic toxicity studies in animals have demonstrated reduced spermatogenesis and testicular atrophy. The effect of Duvalap on the development of the testes, sperm production and fertility in male patients is unknown.

Use in Children

Monotherapy is preferable for children under 3 years of age but, prior to initiation of Duvalap treatment, the potential benefit should be weighed against the possible risk of liver damage in these children. The concomitant use of salicylates should be avoided in such children due to the risk of liver toxicity.

Adverse Reactions

Since valproates have usually been used with other anti-epileptic drugs, in most cases it is not possible to determine whether the following adverse reactions can be ascribed to valproates alone, or to the combination of drugs.

Gastrointestinal

The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy.

Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have been reported.

Central Nervous System

Sedative effects have been noted in patients receiving valproates alone, but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", tremor (may be dose-related), hallucinations, dysarthria, dizziness and in coordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproates alone or in conjunction with phenobarbital. In rare cases encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels, all patients recovered after the drug was withdrawn

Dermatological

Transient increases in hair loss have been observed. Skin rash, petechiae have rarely been noted, erythema multiforme, generalized pruritus, photosensitivity, Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6-month-old infant.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration.

Musculoskeletal

Weakness.

Hematopoietic

Valproates inhibit the secondary phase of platelet aggregation, and this may alter bleeding time. Thrombocytopenia, bruising, hematoma formation and frank hemorrhage, relative lymphocytosis and hypofibrinogenemia, leukopenia, eosinophilia, anemia, acute intermittent porphyria and marrow suppression have also been reported.

The occurrence of vasculitis has been reported.

Hepatic

Minor elevations of transaminases (SGOT and SGPT) and LDH are frequent. They appear to be dose-related. Occasionally, laboratory test results include increase in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity

Endocrine

Irregular menses and secondary amenorrhea, abnormal thyroid function tests and parotid gland swelling. There have been rare reports of breast enlargement and galactorrhoea. Weight increase may occur.

Pancreatic

Acute pancreatitis, including rare fatal cases.

Metabolic

Hyperammonemia, Hyperglycinemia, hyponatremia, inappropriate ADH secretion has been reported and has been associated with a fatal outcome in patients with preexistent nonketotic hyperglycinemia.

Decrease carnitine concentrations have been reported.

Genitourinary

Enuresis and urinary tract infection.

Special senses

Hearing loss, either reversible or irreversible. Ear pain has also been reported.

Other

Edema of extremities, lupus erythematosus and fever.

Precautions

Patients with a previous history of hepatitis, neurological illness associated with epilepsy (such as degenerative or metabolic diseases, especially of a genetic nature), or severe epilepsy with psychic retardation or cerebral lesions, should be kept under close supervision.

Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding time determinations are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving Duvallep be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of Duvallep dosage or withdrawal of therapy pending investigation.

In patients on valproates exhibiting acute painful abdominal syndrome evoking pancreatitis, determination of serum amylase level should be performed, if possible before considering surgical exploration, since the pancreatic disorders generally disappear upon reduction or withdrawal of valproates.

Patients taking this drug should be advised against engaging in potentially hazardous activities requiring mental alertness, such as driving a car or operating machinery, until it can be established whether the medication causes drowsiness.

Hyperammonemia, with or without lethargy or coma, has been reported and may be present in the absence of abnormal liver function tests. If hyperammonemia occurs, valproates should be discontinued.

Since valproates may interact with concurrently administered anti-epileptic drugs, periodic serum level determinations of these drugs are recommended during the early course of therapy.

There have been reports of altered thyroid function tests associated with valproates. The clinical significance of these is unknown.

In patients with renal insufficiency, it may be necessary to decrease dosage because of increase in free serum valproic acid levels.

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

Drug Interactions

Valproates/ Alcohol

Valproates may potentiate the CNS depressant activity of alcohol and benzodiazepines.

Valproates/Other Anticonvulsant Drugs

Neurological side effects may be observed when valproates are administered concomitantly with other anticonvulsant drugs, even without significant elevation of their serum concentrations.

Valproates often cause an increase in serum Phenobarbital levels; the average increase in total serum Phenobarbital levels is 30-60%. Serum barbiturate levels should be obtained, if possible, and the barbiturate dosage decreased if appropriate. The concomitant administration of valproate with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine, dicumarol and phenytoin) may result in alteration of serum drug concentrations.

Primidone is metabolized into a barbiturate and therefore may be involved in a similar or identical interaction.

There is evidence that valproate can cause an increase in serum Phenobarbital concentrations by impairment of non renal clearance. This phenomenon can result in severe CNS depression.

Valproates may produce either an increase or a decrease in total serum concentrations of phenytoin. However, the free fraction of phenytoin generally increases. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproates and clonazepam may produce absence status.

The addition of carbamazepine usually results in a 25-50% decrease in blood valproic acid levels. The addition of phenobarbital or primidone usually results in a 30-50% decrease in blood valproic acid levels.

Therefore, when valproates are used to gradually replace other anticonvulsant drugs, blood valproic acid remains low during the transition state, and then rises markedly when subsequently given alone at the same dosage.

Valproates/Neuroleptics/Monoamine Oxidase Inhibitors/Tricyclic Antidepressants

Valproates potentiate the activity of neuroleptics, monoamine oxidase inhibitors and tricyclic antidepressants. Caution is recommended when using tricyclic antidepressants, because of their convulsant potential.

Valproates/ Drugs Affecting Platelet Aggregation (e.g. aspirin, dipyridamole)

Since valproates may affect platelet function, blood counts including platelets as well as bleeding time determinations, are recommended prior to initiating therapy and at periodic intervals, especially when other drugs affecting platelet aggregation are administered concurrently.

Valproates/ Antivitamin K Levels

Since valproates are usually free from the enzyme induction effect, they do not tend to lower serum Antivitamin K levels. On the contrary, they may increase the free fraction of warfarin as a result of a competitive process at the albumin binding sites.

Valproates/Contraceptives

There is an association between the use of certain antiepileptics and failure of contraceptives. One explanation for this is that enzyme-inducing antiepileptics effectively lower plasma concentrations for the relevant steroid hormones, resulting in unimpaired ovulation. However, other mechanisms, not related to enzyme induction may contribute to the failure of oral contraceptives.

Valproates/ Cimetidine/ Erythromycin

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

Valproates/ Mefloquine

Mefloquine increases valproic acid metabolism and has a convulsant effect; therefore epileptic seizures may occur in cases of combined therapy.

Valproates/ethosuximide

Patients receiving valproate and ethosuximide especially along with anticonvulsants should be monitored for alterations in serum concentrations of both drugs.

Diagnostic Interference

Valproates are partially eliminated in the urine as a keto-metabolite, which may lead to false interpretation of the urine ketone test.

Sodium valproate is eliminated mainly via the kidneys, partly in the form of ketone bodies. This may result in false positive urine tests for possible diabetes.

Dosage and Administration

Duvalap should be taken preferably at the beginning of meals. Tablets should be swallowed completely, if necessary with a little water.

A sugar-free syrup formulation is available for diabetic patients.

Single Drug Therapy

In Previously Untreated Patients

The average daily dosage, usually given in 2 divided doses is:

Newborns, Infants and Children

25 mg /kg body weight.

Adolescents

20-25 mg/kg body weight.

Adult

20 mg/kg body weight.

Elderly

15-20 mg/kg body weight.

Sodium valproate should be introduced gradually. Therapy should start with an initial dose of 10-15 mg/kg body weight/day, and should be increased by 5 mg/kg body weight/day at 5-day or preferably weekly intervals.

Results should be assessed when each of the following doses are reached in single-drug therapy: 15 mg/kg body weight/day in elderly patients, 20 mg/kg body weight/ day in adults and adolescents, 25 mg/kg body weight/ day in children and infants, and after at least 2 or 3 weeks of valproate therapy.

If the clinical efficacy is deemed satisfactory and serum levels are in the recommended range, this dose is maintained. If not, the dosage should be adjusted as required by the clinical, and possibly also the biological, situation.

Doses exceeding 25 mg/kg body weight/day in elderly patients, 30 mg/kg body weight/day in adults and adolescents, 35 mg/kg body weight/day in children and 40 mg/kg body weight/day in infants, are rarely required during single-drug therapy. If they are necessary, it is recommended to give the drug in 3 divided doses per day and to supervise patients more closely, since high serum levels may be achieved.

Combination Therapy

With other Anticonvulsants

The average daily dosage to be administered is generally of the same order as for single-drug therapy. In certain cases, it may be higher by 5-10 mg/kg body weight/day, depending on the clinical, and possibly the biological, situation.

Sodium valproate must be introduced gradually.

The influence of other anticonvulsant medication on valproate therapy should be taken into account. Since serum, valproic acid levels are normally lowered by 25-50% when carbamazepine is administered concomitantly and by almost 30-50% when administered with phenobarbital, in such cases it is not exceptional to find low serum concentrations with the usual sodium valproate dosage.

The influence of valproates on other anticonvulsant medication should also be taken into account. An immediate decrease in barbiturate dosage of 1/3 or even more is required. Without this precaution, the plasma barbiturate concentration might be too high.

Replacement single drug therapy

When sodium valproate is gradually substituted for previous medication, the schedule of introduction is the same as that explained above. The dosages of previous anticonvulsants, especially barbiturates, should be immediately reduced and then progressively withdrawn. This requires 2-8 weeks.

The withdrawal should be more gradual and cautious in the following cases: the patient has been suffering from epilepsy for a long time; the seizures are difficult to control; previous treatment was prolonged and included phenobarbital. Primidone, phenytoin, and/or benzodiazepine derivatives.

Over Dosage

Over Dosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported. Sodium valproate is absorbed very rapidly, so gastric lavage may be of value only in the first 12 hours. It is excreted almost entirely within 24 hours (70% in the urine). General supportive measures are recommended, with special attention to maintaining adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of Duvalep over dosage. However, because naloxone could theoretically also reverse the anti-epileptic effects of Duvalep, it should be used with caution

Pharmaceutical Precautions

Duvalap tablets should be stored in a cool, dry place.

Duvalap solution, syrup and sugar-free syrup should be kept in a cool place, away from direct sunlight

Presentation

Duvalap Tablets 200 mg

Box of 40 enteric-coated tablets

Duvalap Syrup/Duvalap Sugar-Free Syrup

Bottles of 110 ml