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Med Choice CNS

Valproic Acid

Depamax®

250 mg / 5 mL Syrup

ANTIEPILEPTIC

℞

WARNING:

- Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter.
- Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ.
- Pancreatitis, including fatal hemorrhagic cases.

(See Warnings and Precautions for full information.)

FORMULATION:
Each 5 mL contains:
Valproic Acid (as Sodium Valproate), USP……250 mg
(equivalent to 288 mg Sodium Valproate)

PRODUCT DESCRIPTION:
Valproic Acid (Depamax®) 250 mg / 5 mL Syrup is a clear, light red to red homogenous solution with cherry odor and flavor.

PHARMACOLOGIC PROPERTIES
Pharmacodynamics:
Pharmacotherapeutic Group: Antiepileptic
ATC-code: N03AG01
Mechanism of action and pharmacodynamic properties
Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanism by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

Pharmacokinetics:
Absorption / Bioavailability:
Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. The rate of absorption may vary depending on the formulation administered (liquid, solid, or sprinkle), conditions of use (fasting or postprandial) and the method of administration (whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.
Upon initiation of treatment, possible differences among the various valproate products in T_{max} and C_{max} could be important. In single dose studies, the effect of feeding had a greater influence on the rate of absorption of tablets (increase in T_{max} from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).
As the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. The total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Distribution:
Protein Binding
The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg / mL to 18.5% at 130 mcg / mL. With the elderly, patients with chronic hepatic diseases, patients with renal impairment, and in the presence of other drugs (e.g., aspirin), protein binding of valproate is reduced.
CNS Distribution
Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism:
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30%-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15%-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine. Concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding.

Elimination:
Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg. These estimates are primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems.

Special Populations
Effect of age
Neonates
Children within the first two months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding).

Children
Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly
The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26).

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Effect of Gender
There are no differences in the body surface area adjusted unbound clearance between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L / hr per 1.73 m^2, respectively).

Effect of Race
The effects of race on the kinetics of valproate have not been studied.

Effect of Disease
Liver Disease
Liver disease impairs the capacity to eliminate valproate. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate.

Renal Disease
A slight reduction (27%) in the clearance of unbound valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%.

INDICATIONS:
Valproic acid is indicated as monotherapy and adjunctive therapy in the treatment of:
- Complex partial seizures that occur either in isolation or in association with other types of seizures.
- Simple and complex absence seizures.
- Multiple seizure types which include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

DOSAGE AND ADMINISTRATION:
Epilepsy
Valproic Acid (Depamax®) 250 mg/ 5 mL Syrup is intended for oral administration. Patients should be informed to take it every day as prescribed. If a dose is missed, it should be taken as soon as possible, unless it is almost time for the next dose. If the patient skipped a dose, the next dose should not be doubled.

Valproic acid is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the drug's dosage is titrated upward, concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected.

Complex Partial Seizures
For adults and children 10 years of age or older.

Monotherapy (Initial Therapy)
Valproic acid has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. Increase of dosage should be by 5 to 10 mg/kg/week to achieve optimal clinical response. Typically, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

Conversion to Monotherapy
Initial therapy is 15 mg/kg/day that should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Optimal clinical response is achieved at daily doses below 60 mg/kg/day. Plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL) if clinical response has not been achieved. No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of valproic therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy
Valproic Acid may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at one-week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.
Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

The following table is a guide for the initial daily dose of valproic acid (15 mg/kg/day):

Initial Daily Dose Guide					
Weight		Total Daily Dose	Number of Teaspoonfuls of Syrup		
(kg)	(lb)	(mg)	Dose 1	Dose 2	Dose 3
10 – 24.9	22 – 54.9	250	0	0	1
25 – 39.9	55 – 87.9	500	1	0	1
40 – 59.9	88 – 131.9	750	1	1	1
60 – 74.9	132 – 164.9	1,000	1	1	2
75 – 89.9	165 – 197.9	1,250	2	1	2

General Dosing Advice
Dosing in Elderly Patients
It is advisable for the starting dose to be reduced for these patients due to a decrease in unbound valproate clearance and possibly a greater sensitivity to somnolence in the elderly. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

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Dose-Related Adverse Reactions
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males).

G.I. Irritation
Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

CONTRAINDICATIONS:
Valproic acid should not be administered to patients with hepatic disease or significant hepatic dysfunction. It is contraindicated on patients with known sensitivity to the drug and urea cycle disorders.

WARNINGS AND PRECAUTIONS:
Hepatotoxicity
An occurrence of hepatic failure resulting to fatalities in patients receiving valproate during the first 6 months of treatment has been reported. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. A loss of seizure control may also occur for epileptic patient. Close monitoring of patients experiencing these symptoms is needed. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Discontinue the drug immediately in the presence of significant hepatic dysfunction, suspected or apparent. There are some cases wherein in spite of discontinuation, hepatic dysfunction still progressed.

Use in Women of Childbearing Potential
Valproic acid should not be administered to a woman of childbearing potential unless essential to the management of her medical condition as the fetus is at risk of neural tube defects and other major congenital malformations. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). It is also advisable for women to use effective contraception while using valproic acid. This medication should not be discontinued abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life. There are also evidences that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population.

Birth Defects and Neurobehavioral Adverse Effects
Valproate can cause neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, and malformations involving various body systems). Babies born to mothers using valproate has a rate about four times higher on risk of congenital malformations than those babies born to epileptic mothers using other anti-seizure monotherapies. Evidence suggests that the use of folic acid prior to conception and during the first trimester of pregnancy can decrease the risk for congenital neural tube defects in the general population.

Several published epidemiological studies have indicated that those children exposed to valproate inside the uterus have lower cognitive test scores than those exposed to another antiepileptic drugs or without antiepileptic drugs in the uterus. Although all of the available studies have methodological limitations, the weight of the evidence supports the conclusion that valproate exposure in utero causes subsequent adverse effects on cognitive development.

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 rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. Abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. The use of valproate should ordinarily be discontinued once pancreatitis is diagnosed.

Urea Cycle Disorders (UCD)
Valproic acid is contraindicated in patients with known urea cycle disorders.

Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.
The following patients should be evaluated for UCD prior to valproate therapy:
- Those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine.
- Those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance.
- Those with a family history of UCD or a family history of unexplained infant deaths (particularly males).
- Those with other signs or symptoms of UCD.

Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders.

Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. Inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving valproic acid be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

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Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients experiencing unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

Hyperammonemia and Encephalopathy Associated with Concomitant Topiramate Use
Administration of topiramate and valproate concomitantly has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting.

Hypothermia
An unintentional drop in body core temperature to <35°C (95°F) known as hypothermia has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This can also be observed using concomitant topiramate with valproate after starting or increasing the daily dose of topiramate. Patients who develop hypothermia should consider stopping valproate. Hypothermia is usually manifested by lethargy, confusion, coma, and significant alterations in other major organ systems (e.g., cardiovascular and respiratory systems).

Multi-organ Hypersensitivity Reaction
Multi-organ hypersensitivity reactions have been rarely reported in close temporal association after the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritus, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued, and an alternative treatment should be started.

Interaction with Carbapenem Antibiotics
Carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) may reduce serum valproate concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproate concentrations should be monitored frequently after initiating carbapenem therapy. If serum valproate concentrations drop significantly or seizure control deteriorates, alternative antibacterial or anticonvulsant therapy should be considered.

Somnolence in the Elderly
Higher proportion of valproate patients experienced somnolence and dehydration. There was an associated reduced nutritional intake and weight loss. Patients who experienced these events have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN (Blood Urea Nitrogen). In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

Monitoring: Drug Plasma Concentration
Since valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy.

Effect on Ketone and Thyroid Function Tests
Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test. There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Effect on HIV and CMV Viruses Replication
There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

DRUG INTERACTIONS:
Effects of Co-Administered Drugs on Valproate Clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepileptic drugs.

Drugs for which a potentially important interaction has been observed:
Aspirin:
Co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients decreases protein binding and inhibition of metabolism of valproate. Caution should be observed when both the valproate and aspirin are to be co-administered.

Carbapenem Antibiotics:
Patients receiving carbapenem antibiotics show a significant reduction in serum valproic acid concentration. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy.

Felbamate:
The co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin:
A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

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Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Antacids:
Co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine:
A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol:
A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine:
Cimetidine and ranitidine do not affect the clearance of valproate.

Effect of Valproate on Other Drugs
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.

Drugs for which a potentially important valproate interaction has been observed:

Amitriptyline/Nortriptyline:
Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/carbamazepine-10,11-Epoxide
Serum levels of carbamazepine (CBZ) decreased by 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam
The concomitant use of valproate and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam
Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide
Valproate inhibits the metabolism of ethosuximide. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine
The dose of lamotrigine should be reduced when co-administered with valproate. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration.

Phenobarbital
Valproate was found to inhibit the metabolism of phenobarbital. There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate. Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin
In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Primidone
This is metabolized into a barbiturate and therefore, may also be involved in a similar interaction with valproate as phenobarbital.

Propofol
Interaction between propofol and valproate may occur leading to an increased blood level of propofol. Dosing of propofol should be reduced when co-administered with valproate.

Nimodipine
Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50%.

Tolbutamide
From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Topiramate and acetazolamide
Topiramate with valproate has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported. Concomitant administration of valproate and topiramate or acetazolamide has been associated with hyperammonemia and/or encephalopathy.

Warfarin
In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproate therapy is instituted in patients taking anticoagulants.

Zidovudine
In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Quetiapine
Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

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Drugs for which either no interaction or a likely clinically unimportant interaction has been observed

Acetaminophen
Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Clozapine
In psychotic patients, no interaction was observed when valproate was co-administered with clozapine.

Lithium
Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers had no effect on the steady-state kinetics of lithium.

Lorazepam
Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

Rufinamide
Valproic acid may lead to an increase in plasma concentration of rufinamide.

Oral Contraceptive Steroids
Administration of a single-dose of ethinylestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

FERTILITY, PREGNANCY AND LACTATION:
Valproic acid should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated.

Pregnancy Exposure Risk related to Valproate
Abnormal pregnancy outcomes are associated with valproate monotherapy and valproate polytherapy.

Congenital malformations
There is a greater risk of congenital malformations for antiepileptic polytherapy with valproate. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders
Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Female children, female adolescents, and woman of childbearing potential
- If a woman wants to plan a pregnancy.
- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.
- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed.
- Women of childbearing potential have to use effective contraception during treatment.
- If a woman plans a pregnancy or becomes pregnant, valproate therapy should be stopped.
- In women planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy or mania.

If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:
- Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. Prolonged release formulation is preferable to other treatment formulation in order to avoid high peak plasma concentrations.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies however, available evidence does not suggest that it prevents birth defects or malformations due to valproate exposure.
- Institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Prophylaxis of migraine attacks: Valproic acid is contraindicated for prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate. Pregnancy must be excluded before start of treatment with valproate.

Risk in the neonate
Hemorrhagic syndrome has been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia, which may be fatal has also been reported. Cases of hypoglycemia and hypothyroidism have been reported also in neonates whose mothers have taken valproate during pregnancy. Withdrawal syndrome 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. Hematological disorders have been observed in breastfed newborns/infants of treated women. Discontinuance of breastfeeding or divalproex sodium therapy must be decided taking into account the benefit for the breastfeeding child and for the woman.

Fertility
Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate. This may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

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EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

ADVERSE DRUG REACTIONS:

Epilepsy
Complex Partial Seizure (CPS): Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. Primary reason for discontinuation was intolerance.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium in the controlled trials of complex partial seizures:
Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

Other Patient Populations
Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Body System	Adverse Drug Reactions
Gastrointestinal	
Very Common	Nausea, vomiting, indigestion
Common	Diarrhea, abdominal cramps, constipation, gingival disorder (mainly gingival hyperplasia), anorexia, increased appetite
Rare	Obesity
Central Nervous System	
Very Common	Sedative effects
Common	Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, memory impairment, cognitive disorder, and extrapyramidal disorders including parkinsonism, reversible and irreversible cerebral and cerebellar atrophy, congenital malformations, developmental disorders
Uncommon	Aggravated convulsions, sequelae
Rare	Coma, encephalopathy, with or without fever
Dermatologic	
Common	Transient hair loss, hair disorders, skin rash, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson Syndrome, serious skin reactions, nail and nail bed disorders
Rare	Toxic epidermal necrolysis
Psychiatric	
Common	Emotional upset, depression, psychosis, aggression, psychomotor, hyperactivity, hostility, agitation, disturbance in attention, abnormal behavior, learning disorder and behavioral deterioration
Musculoskeletal	
Common	Weakness, osteoporosis, osteopenia
Hematologic	
Common	Thrombocytopenia, petechiae, bruising, hematoma formation, epistaxis, hemorrhage, relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis and acute intermittent porphyria
Hepatic	
Common	Minor elevation of transaminase, LDH
Rare	Hepatotoxicity
Endocrine	
Common	Irregular menses, secondary amenorrhea, breast enlargement, parotid gland swelling, galactorrhea, hyperandrogenism, hypothyroidism
Rare	Polycystic ovary
Pancreatic	
Common	Acute pancreatitis
Metabolic	
Common	Hyperammonemia, hyponatremia, inappropriate ADH secretion, decreased carnitine, hyperglycinemia, insulin resistance, dyslipidemia
Rare	Fanconi's syndrome
Genitourinary	
Common	Enuresis, renal failure, tubulointerstitial nephritis, urinary tract infection
Reproductive	
Common	Azoospermia, abnormal semen analysis, decreased sperm count, abnormal spermatozoa morphology, aspermia, decrease spermatozoa motility
Special Senses	
Common	Hearing loss, either reversible or irreversible, ear pain
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Common	Myelodysplastic syndrome
Respiratory, thoracic and mediastinal disorders	
Common	Pleural effusion
Other	
Common	Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, rhabdomyolysis, biotin deficiency/biotinidase deficiency, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever and hypothermia

Mania
Although valproic acid have not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more patients from two placebo-controlled clinical trials of divalproex sodium tablets:
Body as a whole: Chills, neck pain, neck rigidity
Cardiovascular System: Hypotension, postural hypotension, vasodilation
Digestive System: Fecal incontinence, gastroenteritis, glossitis
Musculoskeletal System: Arthrosis
Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo
Skin and Appendages: Furunculosis, maculopapular rash, seborrhea
Special Senses: Conjunctivitis, dry eyes, eye pain
Urogenital System: Dysuria
Other patient population: Extrapyramidal disorders, encephalopathy

Migraine
Although valproic acid have not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine, the following adverse events not listed above were reported by 1% or more patients from two placebo-controlled clinical trials of divalproex sodium tablets:
Body as whole: Face edema
Digestive System: Dry mouth, stomatitis
Urogenital System: Cystitis, metrorrhagia, vaginal hemorrhage
Other patient populations: Encephalopathy

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction."

OVERDOSAGE AND TREATMENT:
Valproate overdosage may result in somnolence, heart block and deep coma. Though fatalities have been reported, patients have recovered from valproate as high as 2120 mcg/mL. Hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug in overdose situations. It has been reported that naloxone can also help reverse the CNS depressant effects of valproate because it could theoretically reverse the antiepileptic effect of valproate provided, however it would be used with caution in patients with epilepsy.

STORAGE CONDITION:
Valproic Acid (as Sodium Valproate) 250 mg / 5 mL Syrup (Depamax®) should be stored at temperatures not exceeding 30°C.
Keep out of reach of children.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Valproic Acid (as Sodium Valproate)
250 mg / 5 mL Syrup (Depamax®).....Boston Round Amber Bottle x 120 mL fitted With 22 mm Foam-lined PP Aluminum Cap With PSP Liner (Box x 1's)

Registration No.: DRP-16006
Date of First Authorization: October 2024
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Manufactured for:
MEDCHOICE CNS PHARMA CORPORATION
Unit 1001, 88 Corporate Center, Valero corner Sedeño Streets, Salcedo Village, Makati, Metro Manila

Manufactured by:
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