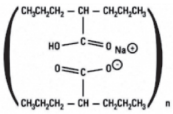
PRESCRIBING INFORMATION: For the use of a Psychiatrist/Neurologists only.

DIVAA SOLUTION 500

Divalproex Sodium Oral Solution 100 mg/ml

COMPOSITION
Each 5 ml contains:
Divalproex sodium IP equivalent to
Valproic acid 500 mg
Flavoured sugar free base Q.S.

DESCRIPTION
Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis (2- propylpentanoate). Divalproex sodium has the following structure:



CLINICAL PHARMACOLOGY
Pharmacodynamics
Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms 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:
Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation, the conditions of use (e.g., fasting or postprandial) and the method of administration, these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy. In single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (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). Any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

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. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide).

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 - 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.

Elimination:
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/hr/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250-1000 mg. Patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic drug concentrations should be intensified whenever concomitant antiepileptic drugs are introduced or withdrawn.

INDICATIONS
As a monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures for adult patients only.

DOSAGE AND ADMINISTRATION
Epilepsy
Divalproex sodium solution is administered orally. As the divalproex sodium dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected.

Complex Partial Seizures
Monotherapy (Initial therapy)
Divalproex sodium has not been systematically studied as initial therapy. Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/week to achieve optimal clinical response. Ordinarily, 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 (50-100 mcg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

Conversion to monotherapy
Concomitant antiepileptic drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium therapy, or delayed by 1-2 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
In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy.

Simple and Complex Absence Seizures: The recommended initial dose is 15 mg/kg/day, increasing at weekly intervals by 5-10 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 500 mg, it should be given in divided doses.

CONTRAINDICATIONS
Divalproex sodium should not be administered to patients with hepatic disease of significant hepatic dysfunction. It is contraindicated in patients with known hypersensitivity to the drug and in patients with known urea cycle disorders.

WARNINGS AND PRECAUTIONS
- Hepatotoxicity; evaluate high risk populations and monitor serum liver tests.
- Birth defects and decreased IQ following *in utero* exposure; only use to treat pregnant women with epilepsy if other medications are unacceptable; should not be administered to a woman of childbearing potential unless essential.
- Pancreatitis; DIVAA SOLUTION 500 should ordinarily be discontinued.
- Brain Atrophy; evaluate for continued use in the presence of suspected or apparent signs of reversible or irreversible cerebral and cerebellar atrophy.
- Suicidal behavior or ideation; Antiepileptic drugs, including DIVAA SOLUTION 500, increase the risk of suicidal thoughts or behavior.
- Thrombocytopenia; monitor platelet counts and coagulation tests.
- Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation of valproate therapy.
- Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate.
- Multi-organ hypersensitivity reaction; discontinue DIVAA SOLUTION 500.
- Somnolence in the elderly can occur. DIVAA SOLUTION 500 dosage should be increased slowly and with regular monitoring for fluid and nutritional intake.

Urea Cycle Disorders
divalproex is contraindicated in patients with known urea cycle disorders (UCD).
Prior to the initiation of DIVAA SOLUTION 500 therapy, evaluation for UCD should be considered in the following patients:
1) those with a history of unexplained encephalopathy or coma;
2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance;
3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);
4) those with other signs or symptoms of UCD.

Monitoring: Drug Plasma Concentration
Since valproic acid 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.

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. 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.

Special Populations
Pregnancy
Use of divalproex during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

INTAS	AW No./AW Code :	WND DIVAA500 SOLN PI 02		
	Size :	150 x 210 (mm) Front Side		
Pantone No. :	Black			
Date :	21/11/18			
Checked by :	Packaging Dev.	Packaging Dev.	C.Q.A.	Approved by C.Q.A.
Signature & Date				

Antiepileptic drugs should be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their seizures.

Nursing Mothers
Valproate is excreted in breast milk. It is not known what effect this would have on a nursing infant. Caution should be exercised when divalproex sodium is administered to a nursing woman.

Pediatric Use
There is no data on the use of Divalproex solution in pediatric patients.
However the use of divalproex sodium tablets (250 mg/500 mg) and valproic acid solution (250 mg/5 ml) is approved and well documented in epileptic adults and children above 10 years, with an accepted safety profile.

Geriatric Use
A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. The starting dose should be reduced in these patients, and dosage should be increased more slowly and with monitoring for possible adverse events.

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 (2-2.6 fold increases) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease, whereas total concentrations may appear to be normal.

Renal Disease: A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance <10 ml/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

DRUG INTERACTIONS
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyl transferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate.
Aspirin: In pediatric patients, aspirin in antipyretic doses may decrease protein binding and inhibit metabolism of valproate. Valproate free fraction may increase in the presence of aspirin compared to valproate alone. Whether or not this interaction observed in children applies to adults is unknown, but caution should be observed if valproate and aspirin are to be co-administered.
Felbamate: A decrease in valproate dosage may be necessary when felbamate therapy is initiated.
Rifampin: Valproate dosage adjustment may be necessary when it is coadministered with rifampin.
Chlorpromazine: Chlorpromazine may increase trough plasma levels of valproate on concomitant medication.
Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase and glucuronyl transferases.
Clonazepam: The concomitant use of valproic acid 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.
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 coadministered with valproate.
Phenobarbital: Valproate is found to inhibit the metabolism of phenobarbital. All patients receiving concomitant barbiturate therapy should be closely monitored for neurologic toxicity.
Primidone: Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.
Phenytoin: Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. The dosage of phenytoin should be adjusted as required by the clinical situation.
Tolbutamide: In vitro experiments show that the unbound fraction of tolbutamide increases when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.
Warfarin: Coagulation tests should be monitored if divalproex therapy is instituted in patients taking anticoagulants.
Zidovudine: On concomitant administration with valproate, the clearance of zidovudine may decrease.
Amitriptyline/Nortriptyline: Administration of amitriptyline in patients receiving valproate may result in a decrease in plasma clearance of amitriptyline.
Lorazepam: Concomitant administration of valproate and lorazepam may decrease the plasma clearance of lorazepam.
Carbapenems: Carbapenem antibiotics (ertapenem, imipenem, meropenem) may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates.

ADVERSE EFFECTS
Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically.
Common side effects: of valproic acid are nausea, drowsiness, and dizziness; but for some patients these conditions lessen or go away over time. Because valproic acid may cause drowsiness, patients receiving this medication should not engage in activities that are possibly dangerous (for example, driving a motor vehicle) while undergoing treatment until the drowsiness goes away.

Following are the side effects profile as summarized here under:
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.
Hepatic system: Liver problems, which are rarely severe, may develop on valproic acid, especially in the first six months of treatment. Blood tests to monitor liver function are an important part of treatment with valproic acid, in order to make sure that you are safe. Rarely, a potentially fatal swelling of the pancreas (called pancreatitis) and Fanconi's syndrome can also occur.
Hyperammonemia: Valproic acid may occasionally cause an increase in your blood levels of ammonia. If this happens, patients may get confused, disoriented, or have difficulty thinking. Blood tests can be used to check the amount of ammonia in your blood and ensure safety of this medication.
Hematopoetic system: Problems with low levels of white blood cell count and blood platelets, which are rarely severe, may also happen while taking this medication. Blood tests are used to check for this side effect.
Skin and appendages: Occasionally, there may be rashes, and rarely, hirsutism, acne, toxic epidermal necrolysis and Stevens-Johnson syndrome or erythema multifome. Transient hair loss, sometimes with regrowth of curly hair, has occurred. Irregular periods, amenorrhoea, and gynaecomastia have been reported rarely.
Stopping valproic acid quickly may lead to having a seizure. Do not stop taking valproic acid without discussing it with your healthcare provider.

Long term side-effects:
Patients taking valproic acid for a long time may suffer from the following side effects:
Weight gain
Hairloss
Right sided stomach pain, severe nausea/vomiting, facial swelling, yellowing of the skin and pale stools, these may be signs of liver problems

OVERDOSAGE
Overdosage with valproate may result in somnolence, heart block, and deep coma.
Fatalities have been reported; however, patients have recovered from valproate levels as high as 2120 g/ml.
In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of the drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.
Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

STORAGE
Store in well-closed container, at a temperature not exceeding 30°C.
Keep out of reach of children.

PRESENTATION
DIVAA SOLUTION 500 is available in 100 ml bottle with gradation cap for dosing.

Manufactured by:
Windlas Biotech Private Limited
(Plant-2), Khasra No. 141 to 143 & 145,
Mohabewala Industrial Area,
Dehradun - 248 110, Uttarakhand.

Marketed by:
INTAS
INTAS PHARMACEUTICALS LTD.
Matoda-382 210, Dist.: Ahmedabad, INDIA

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