

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

1. Product name

1

UNIPROEX ER 500 (Divalproex Sodium Extended-Release Tablets USP 500 mg)

1. Strength

2

500 mg

1. Pharmaceutical Dosage form

3

Tablet

1. Distribution Category

4

Prescription Only Medicine (POM)

2. Qualitative and Quantitative Composition

Each Extended-Release Tablet Contains:

Divalproex Sodium USP equivalent to Valproic acid 500 mg

Excipient(s) with known effect:

Lactose Monohydrate16.878 mg (see section 4.4)

For Full list of Excipients see section 6.1

3. Pharmaceutical Form

Extended-Release Tablets

Yellow colored, oval shaped, biconvex film coated tablets imprinted with "U 381" on one side and plain on the other.

4. Clinical particulars

4. Therapeutic indications

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Mania

Divalproex sodium extended-release tablets are valproate and are indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of divalproex sodium extended-release tablets is based in part on studies of divalproex sodium delayed-release tablets in this indication, and was confirmed in a 3-week trial with patients meeting DSM-IV TR criteria for bipolar I disorder, manic or mixed type, who were hospitalized for acute mania.

The effectiveness of valproate for long-term use in mania, i.e., more than 3 weeks, has not been demonstrated in controlled clinical trials. Therefore, healthcare providers who elect to use divalproex sodium extended-release tablets for extended periods should continually reevaluate the long-term risk-benefits of the drug for the individual patient.

Epilepsy

Divalproex sodium extended-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium extended-release tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that 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.

Migraine

Divalproex sodium extended-release tablets are indicated for prophylaxis of migraine headaches. There is no evidence that divalproex sodium extended-release tablets are useful in the acute treatment of migraine headaches.

Important Limitations

Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide

4 . Posology and method of administration

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Divalproex sodium extended-release tablets are an extended-release product intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.

Mania

Divalproex sodium extended-release tablets are administered orally. The recommended initial dose is 25 mg/kg/day given once daily. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect and the desired range of plasma concentrations. In a placebo-controlled clinical trial of patients with mania or mixed type, patients were dosed to a clinical response with a trough plasma concentration between 85 and 125 mcg/mL. The maximum recommended dosage is 60 mg/kg/day.

There is no body of evidence available from controlled trials to guide a clinician in the long-term management of a patient who improves during divalproex sodium extended-release tablets treatment of an acute manic episode. While it is generally agreed that long-term pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no data to support the benefits of divalproex sodium extended-release tablets in such long-term treatment (i.e., beyond 3 weeks).

Epilepsy

Divalproex sodium extended-release tablets are administered orally, and must be swallowed whole. As divalproex sodium extended-release tablets dosage is titrated up, the plasma 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)

Divalproex sodium extended-release tablets have not been systematically studied as monotherapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 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 to 100 mcg/mL). A recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day should be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 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

4 . Contraindications

3

Divalproex sodium extended-release tablets should not be administered to patients with hepatic disease or significant hepatic dysfunction.

Divalproex sodium extended-release tablets are contraindicated in patients known to have mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (POLG) (Pearlman-Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder.

Divalproex sodium extended-release tablets are contraindicated in patients with known hypersensitivity to the drug.

Divalproex sodium extended-release tablets are contraindicated in patients with known cardiac cycle disorders.

For use in prophylaxis of migraine headaches: Divalproex sodium extended-release tablets are contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

4 . Precautions for use

4

Hepatotoxicity

General Information on Hepatotoxicity: Hepatic failure resulting in fatalities has occurred in patients receiving valproate. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for the appearance of these symptoms. Serum liver tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months of valproate therapy. However, healthcare providers should not rely totally on serum biochemistry since the results may not be abnormal in all instances, but should also consider the results of careful physical examination, medical history and physical examination.

Caution should be observed when administering valproate products to patients with a history of hepatic disease. Patients on multiple anticonvulsants, children, those with certain metabolic disorders, those with severe seizure disorders accompanied by mental retardation and those with organic brain disease may be at particular risk. See below, "Patients with Known or Suspected Mitochondrial Disease."

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 divalproex sodium extended-release tablets are used in this patient population, they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. In progressively older patient groups experience in epilepsy, it has been indicated that the incidence of fatal hepatotoxicity decreases considerably.

Patients with Known or Suspected Mitochondrial Disease

Divalproex sodium extended-release tablets are contraindicated in patients with known mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurodegenerative syndromes caused by mutations in the gene for mitochondrial DNA polymerase gamma (e.g., Alpers- Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.

POLG-related disorders should be suspected in patients with a family history or symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, isolated cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. Mutation testing should be performed in accordance with current clinical practice guidelines for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders.

In patients over two years of age who are clinically suspected of having a mitochondrial disease, divalproex sodium extended-release tablets should only be used if other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with divalproex sodium extended-release tablets for the development of acute liver injury with regular clinical assessments and serum liver test monitoring.

4.5 Interaction with other medicinal products and other forms of 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 (such as ritonavir), may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (and primidone) can double the clearance of valproate. Thus, patients on monotherapy with valproate generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, especially antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed: Aspirin. A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β -oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Whether or not the interaction observed in this study applies to adults is unknown, but caution should be observed if valproate and aspirin are to be co-administered.

Carbapenem Antibiotics

A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (for example, ertapenem, imipenem, meropenem; this is not a complete list) and may result in loss of seizure control. The mechanism of this interaction is not well understood. 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.

Estrogen-Containing Hormonal Contraceptives

Estrogen-containing hormonal contraceptives may increase the clearance of valproate which may result in decreased concentration of valproate and potentially increase seizure frequency. Prescribers should monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products.

Felbamate

A study involving the co-administration of 1,200 mg/day of felbamate with valproate patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/ml) compared to valproate alone.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes of women exposed to antiepileptic drugs (AEDs), including divalproex sodium extended-release tablets, during pregnancy.

Risk Summary

For use in prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

For use in epilepsy or bipolar disorder, valproate should not be used in women who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. Women with epilepsy who become pregnant while taking valproate should discontinue valproate abruptly, as this can precipitate status epilepticus with resultant fetal hypoxia and threat to life.

Maternal valproate use during pregnancy for any indication increases the risk of congenital malformations, particularly neural tube defects including spina bifida, as well as also malformations involving other body systems (e.g., craniofacial defects, cleft lip and palate, oral clefts, cardiovascular malformations, hypospadias, limb malformations). The risk is dose-dependent; however, a threshold dose below which no risk exists has not been established. In utero exposure to valproate may also result in hearing impairment and hearing loss. Valproate polytherapy with other AEDs has been associated with an increased frequency of congenital malformations compared with AED monotherapy. The risk of major structural abnormalities is greatest during the first trimester of pregnancy. Other serious developmental effects can occur with valproate use during pregnancy. The rate of congenital malformations among babies born to mothers who used valproate during pregnancy has been shown to be higher than the rate among babies born to epileptic mothers who used other seizure monotherapies.

Epidemiological studies have indicated that children exposed to valproate in utero have lower IQ scores and a higher risk of neurodevelopmental disorders compared to children exposed to either another AED in utero or to no AEDs in utero.

An observational study has suggested that exposure to valproate during pregnancy increases the risk of autism spectrum disorders.

In animal studies, valproate administration during pregnancy resulted in congenital malformations similar to those seen in humans and neurobehavioral effects in offspring at clinically relevant doses.

There have been reports of hypoglycemia in neonates and fatal cases of neonatal death in infants following maternal use of valproate during pregnancy.

Pregnant women taking valproate may develop hepatic failure or clotting abnormalities including thrombocytopenia, hypofibrinogenemia, and/or decrease in prothrombin time.

4.7 Effects on ability to drive and use machine

The ability to drive or operate machinery may be impaired in patients with clinical symptoms of amiodarone-induced eye disorders.

4.8 Undesirable effects

The following serious adverse reactions are described below and elsewhere in 1 labeling:

Hepatic failure

Birth defects

Decreased IQ following in utero exposure

Pancreatitis

Hyperammonemic encephalopathy

Suicidal behavior and ideation

Bleeding and other hematopoietic disorders

Hypothermia

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorg hypersensitivity reactions

Somnolence in the elderly

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared rates in the clinical studies of another drug and may not reflect the rates observed practice.

Mania

The incidence of treatment-emergent events has been ascertained based on combin data from two three-week placebo-controlled clinical trials of divalproex sodi extended-release tablets in the treatment of manic episodes associated with bipo disorder.

Table 3 summarizes those adverse reactions reported for patients in these trials wh the incidence rate in the divalproex sodium extended-release tablets-treated group w greater than 5% and greater than the placebo incidence.

Table 3. Adverse Reactions Reported by > 5% of Divalproex Sodium Extended Release Tablets-Treated Patients During Placebo-Controlled Trials of Acute Mania¹

Adverse Event Divalproex Sodium Extended-Release Tablets

	(n = 338)		(n = 263)	
	%	Placebo	%	
Somnolence	26	14		
Dyspepsia	23	11		
Nausea	19	13		
Vomiting	13	5		
Diarrhea	12	8		
Dizziness	12	7		
Pain	11	10		
Abdominal Pain		10	5	
Accidental Injury		6	5	
Asthenia	6	5		
Pharyngitis	6	5		

¹The following adverse reactions/event occurred at an equal or greater incidence placebo than for divalproex sodium extended-release tablets: headache

4.9 Overdose and special antidotes

Over dosage with valproate may result in somnolence, heart block, deep coma, and hypernatremia. Fatalities have been reported; however, patients have recovered from valproate levels as high as 2,120 mcg/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 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 overdose. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Anti-epileptic

ATC Code: N03AG01

Pharmacodynamics

Mechanism of Action

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).

Pharmacodynamics

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate may not provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 mcg/mL to 18% at 130 mcg/mL. Higher than expected free fractions occur in the elderly, hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy

The therapeutic range in epilepsy is commonly considered to be 50 to 100 mcg/mL total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Mania

In placebo-controlled clinical trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 85 and 125 mcg/mL.

5.2 Pharmacokinetic Properties

Absorption/Bioavailability

The absolute bioavailability of divalproex sodium extended-release tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion.

When given in equal total daily doses, the bioavailability of divalproex sodium extended-release tablets is less than that of divalproex sodium delayed-release tablets. In five multiple-dose studies in healthy subjects (N=82) and in subjects with epilepsy (N=86), when administered under fasting and nonfasting conditions, divalproex sodium extended-release tablets given once daily produced an average bioavailability of 89% relative to an equal total daily dose of divalproex sodium delayed-release tablets given BID, TID, or QID. The median time to maximum plasma valproate concentrations (C_{max}) after divalproex sodium extended-release tablet administration ranged from 4 to 17 hours. After multiple once-daily dosing of divalproex sodium extended-release tablets, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium delayed-release tablets given BID, TID, or QID.

Conversion from Divalproex Sodium Delayed-Release Tablets to Divalproex Sodium Extended-Release Tablets

When divalproex sodium extended-release tablets are given in doses 8 to 20% higher than the total daily dose of divalproex sodium delayed-release tablets, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of divalproex sodium delayed-release tablets were compared to 8 to 20% higher once-daily doses of divalproex sodium extended-release tablets. In these two studies, divalproex sodium extended-release tablets and divalproex sodium delayed-release tablets regimens were equivalent with respect to area under the curve (AUC; measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for divalproex sodium extended-release tablets relative to divalproex sodium delayed-release tablets regimens (see Table 8).

Table 8. Bioavailability of Divalproex Sodium Extended-Release Tablets Relative to Divalproex Sodium Delayed-release Tablets When Divalproex Sodium Extended-Release Tablets Dose is 8 To 20 % Higher

Study Population	Regimens	Relative Bioavailability
Healthy Volunteers (N=35)	Divalproex sodium extended-release tablets vs 875 & 1,200 mg divalproex sodium delayed-release tablets	AUC 1.059 C _{max} 0.882 C _{min} 1.173
	1,000 & 1,500 mg divalproex sodium extended-release tablets vs 875 & 1,200 mg divalproex sodium delayed-release tablets	1.059 0.882 1.173
Patients with epilepsy on concomitant enzyme-inducing antiepilepsy drugs (N = 64)	1,000 to 5,000 mg divalproex sodium extended-release tablets vs 875 to 4,250 mg divalproex sodium delayed-release tablets	1.008 0.899 1.022
	1,000 to 5,000 mg divalproex sodium extended-release tablets vs 875 to 4,250 mg divalproex sodium delayed-release tablets	1.008 0.899 1.022

Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepin, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between divalproex sodium delayed-release tablets and divalproex sodium extended-release tablets.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Valproate was administered orally to rats and mice at doses of 80 and 170 mg/kg/c (less than the maximum recommended human dose on a mg/m² basis) for two years. The primary findings were an increase in the incidence of subcutaneous fibrosarcoma in high-dose male rats receiving valproate and a dose-related trend for benign pulmonary adenomas in male mice receiving valproate.

Mutagenesis

Valproate was not mutagenic in an in vitro bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an in vivo cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate; this association was not observed in another study conducted in adults.

Impairment of Fertility

In chronic toxicity studies in juvenile and adult rats and dogs, administration of valproate resulted in testicular atrophy and reduced spermatogenesis at oral doses of 400 mg/kg/day or greater in rats (approximately equal to or greater than the maximum recommended human dose (MRHD) on a mg/m² basis) and 150 mg/kg/day or greater in dogs (approximately equal to or greater than the MRHD on a mg/m² basis). Fertility studies in rats have shown no effect on fertility at oral doses of valproate up to 350 mg/kg/day (approximately equal to the MRHD on a mg/m² basis) for 60 days.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose Monohydrate, Ethyl cellulose, Hypromellose, Colloidal Silicon Dioxide, Talc, Stearic Acid, Opadry II 32K520229 Yellow, Opacode Black S-1-277001, Isopropyl Alcohol and Purified water.

Opadry II 32K520229 Yellow contains: Hypromellose, Lactose Monohydrate, Titanium Dioxide, Triacetin and Yellow Iron Oxide.

Imprinting Ink - Opacode S-1-277001 contains: Shellac Glaze, Ferrosoferric Oxide, Butyl Alcohol, Purified Water, Propylene Glycol, Dehydrated Ethanol and Isopropyl Alcohol.

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30° C. Protect from light and moisture.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

A blister of (ALU-ALU) and (Aclar- PVC) foil. 10 tablets are packed in this blister, su
3 Blister/s & a leaflet in turn are packed in carton/s.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with loc
requirements.

7. Marketing Authorization Holder

Unichem Laboratories Limited
Unichem Bhavan, Prabhat Estate,
S.V. Road, Jogeshwari (West)
Mumbai – 400102, INDIA

8. Marketing Authorization Number

TAN 22 HM 0509

9. Date of first authorization/renewal of the authorization

05th December, 2022

10. Date of revision of the text