SUMMARY OF PRODUCT CHARACTRISTICS

1. Name of the Medicinal Product

1.1 Product name

UNIPROEX ER 250 (Divalproex Sodium Extended-Release Tablets USP 250 mg)

1.2 Strength

250 mg

1.3 Pharmaceutical Dosage form

Tablet

1.4 Distribution Category

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 Monohydrate ….16.878 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 380” on one side and plain on the other.

4. Clinical particulars

4. Therapeutic indications

1

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
2

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

Mania
Divalproex sodium extended-release tablets are administered orally. The recomme initial dose is 25 mg/kg/day given once daily. The dose should be increased as rapic possible to achieve the lowest therapeutic dose which produces the desired clinical effe the desired range of plasma concentrations. In a placebo-controlled clinical trial of a mania or mixed type, patients were dosed to a clinical response with a trough pl concentration between 85 and 125 mcg/mL. The maximum recommended dosage is 6(kg/day.

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

Epilepsy
Divalproex sodium extended-release tablets are administered orally, and must be swall whole. As divalproex sodium extended-release tablets dosage is titrated upv concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutar 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 therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage shoul increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, op clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory cl response has not been achieved, plasma levels should be measured to determine wh or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL) recommendation regarding the safety of valproate for use at doses above 60 mg/kg/da be made.

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

Conversion to Monotherapy
Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical respo achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has no

4 . Contraindications
3

Divalproex sodium extended-release tablets should not be administered to pati
hepatic disease or significant hepatic dysfunction.
Divalproex sodium extended-release tablets are contraindicated in patients knowr
mitochondrial disorders caused by mutations in mitochondrial DNA polymerase γ (PO
Alpers-Huttenlocher Syndrome) and children under two years of age who are sus
having a POLG-related disorder.
Divalproex sodium extended-release tablets are contraindicated in patients wit
hypersensitivity to the drug.
Divalproex sodium extended-release tablets are contraindicated in patients with kn
cycle disorders.
For use in prophylaxis of migraine headaches: Divalproex sodium extended-releas
are contraindicated in women who are pregnant and in women of childbearing pote
are not using effective contraception.

4 . Precautions for use
4

Hepatotoxicity

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

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

Experience has indicated that children under the age of two years are at a cor increased risk of developing fatal hepatotoxicity, especially those with the aforen conditions. When divalproex sodium extended-release tablet are used in this patient should be used with extreme caution and as a sole agent. The benefits of therapy s weighed against the risks. In progressively older patient groups experience in epil 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 knowr mitochondrial disorders caused by POLG mutations and children under two years of are clinically suspected of having a mitochondrial disorder. Valproate-induced a failure and liver-related deaths have been reported in patients with hereditary neuro syndromes caused by mutations in the gene for mitochondrial DNA polymerase v (e.g., Alpers- Huttenlocher Syndrome) at a higher rate than those without these sy Most of the reported cases of liver failure in patients with these syndromes ha identified in children and adolescents.

POLG-related disorders should be suspected in patients with a family history or s symptoms of a POLG-related disorder, including but not limited to une encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at pres developmental delays, psychomotor regression, axonal sensorimotor neuropathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aur mutation testing should be performed in accordance with current clinical practic diagnostic evaluation of such disorders. The A467T and W748S mutations are p 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 h mitochondrial disease, divalproex sodium extended-release tablets should only be u other anticonvulsants have failed. This older group of patients should be closely m during treatment with divalproex sodium extended-release tablets for the develo 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 th elevate levels of glucuronosyltransferases (such as ritonavir), may increase t clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (primidone) can double the clearance of valproate. Thus, patients on monotherapy v generally have longer half-lives and higher concentrations than patients receivi polytherapy with ant epilepsy drugs.

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

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

The following list provides information about the potential for an influence of seve commonly prescribed medications on valproate pharmacokinetics. The list is r exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed Aspirin A stu involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) w 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 t presence of aspirin compared to valproate alone. The β-oxidation pathway consisting 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased fr 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspir Whether or not the interaction observed in this study applies to adults is unknown, b 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 report in patients receiving carbapenem antibiotics (for example, ertapenem, imipene meropenem; this is not a complete list) and may result in loss of seizure control. T mechanism of this interaction is not well understood. Serum valproic ac concentrations should be monitored frequently after initiating carbapenem thera Alternative antibacterial or anticonvulsant therapy should be considered if seru valproic acid concentrations drop significantly or seizure control deteriorates.

Estrogen-Containing Hormonal Contraceptives

Estrogen-containing hormonal contraceptives may increase the clearance of valproa which may result in decreased concentration of valproate and potentially increas seizure frequency. Prescribers should monitor serum valproate concentrations a 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 pe concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alor

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcc exposed to antiepileptic drugs (AEDs), including divalproex sodium ex tablets, during pregnancy.

Risk Summary

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

For use in epilepsy or bipolar disorder, valproate should not be used who are pregnant or who plan to become pregnant unless other me failed to provide adequate symptom control or are otherwise unacce with epilepsy who become pregnant while taking valproate should r valproate abruptly, as this can precipitate status epilepticus with resultin fetal hypoxia and threat to life.

Maternal valproate use during pregnancy for any indication increas congenital malformations, particularly neural tube defects including s also malformations involving other body systems (e.g., craniofacial de oral clefts, cardiovascular malformations, hypospadias, limb malformatic dose-dependent; however, a threshold dose below which no risk ex established. In utero exposure to valproate may also result in hearing hearing loss. Valproate polytherapy with other AEDs has been assc increased frequency of congenital malformations compared with AED The risk of major structural abnormalities is greatest during the first trim other serious developmental effects can occur with valproate u pregnancy. The rate of congenital malformations among babies bc mothers who used valproate during pregnancy has been shown to be a higher than the rate among babies born to epileptic mothers who u seizure monotherapies.

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

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

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

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

Pregnant women taking valproate may develop hepatic failure or clottin including thrombocytopenia, hypofibrinogenemia, and/or decrease in ot

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

The following serious adverse reactions are described below and elsewhere in t 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, adver 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 sodiu 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 whe 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 Extende Release Tablets-Treated Patients During Placebo-Controlled Trials of Acute Mania1

Adverse Event	Divalproex Sodium Extended-Release Tablets (n = 338) %	Placebo (n = 263) %
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, a hypernatremia. Fatalities have been reported; however, patients have recovered fr valproate levels as high as 2,120 mcg/mL.

In overdose situations, the fraction of drug not bound to protein is high a hemodialysis or tandem hemodialysis plus hem perfusion may result in significa removal of drug. The benefit of gastric lavage or emesis will vary with the time sir ingestion. General supportive measures should be applied with particular attention the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate o dosage. Because naloxone could theoretically also reverse the antiepileptic effects 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. T mechanisms by which valproate exerts its therapeutic effects have not be established. It has been suggested that its activity in epilepsy is related to increas brain concentrations of gamma-aminobutyric acid (GABA).

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

For example, because the plasma protein binding of valproate is concentrati dependent, the free fraction increases from approximately 10% at 40 mcg/mL to 18.5 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 plası concentrations.

Mania
In placebo-controlled clinical trials of acute mania, patients were dosed to clini 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 table administered as a single dose after a meal was approximately 90% relative intravenous infusion.

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

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

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

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

Study Population	Regimens	Relative Bioavailability		
	Divalproex sodium extended-release tablets vs divalproex sodium delaye release tablets	AUC24	Cmax	Cmin
Healthy Volunteers				
(N=35)	1,000 & 1,500 mg divalproex sodium extended-release tablets vs 875 & 1,2 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 8 to 4,250 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 isozyr system did not significantly alter valproate bioavailability when converting betwe divalproex sodium delayed-release tablets and divalproex sodium extended-relea 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/d (less than the maximum recommended human dose on a mg/m2 basis) for two yea The primary findings were an increase in the incidence of subcutaneous fibrosarcom in high-dose male rats receiving valproate and a dose-related trend for beni pulmonary adenomas in male mice receiving valproate.

Mutagenesis
Valproate was not mutagenic in an in vitro bacterial assay (Ames test), did not produ dominant lethal effects in mice, and did not increase chromosome aberration frequer in an in vivo cytogenetic study in rats. Increased frequencies of sister chroma exchange (SCE) have been reported in a study of epileptic children taking valproa 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 valproate resulted in testicular atrophy and reduced spermatogenesis at oral doses 400 mg/kg/day or greater in rats (approximately equal to or greater than the maximu recommended human dose (MRHD) on a mg/m2 basis) and 150 mg/kg/day or grea in dogs (approximately equal to or greater than the MRHD on a mg/m2 basis). Ferti studies in rats have shown no effect on fertility at oral doses of valproate up to 350 n 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, Ethylcellulose, Hypromellose, Colloidal Silicon Dioxide, Ta Stearic Acid, Opadry II 32K520229 Yellow, Opacode Black S-1-277001, Isoprop Alcohol and Purified water.

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

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

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30º 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 0508

9. Date of first authorization/renewal of the authorization

05th December, 2022

10. Date of revision of the text