Safety Data Sheet
Divalproex Sodium Delayed-Release Tablets USP

Strength: 125/250/500mg. **Pack Size:** Bottles of 100/500 Tablets **Revision No.:** 02

EMERGENCY OVERVIEW

Each Divalproex sodium Delayed-Release Tablet intended for oral administration contains Divalproex sodium equivalent to valproic acid and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

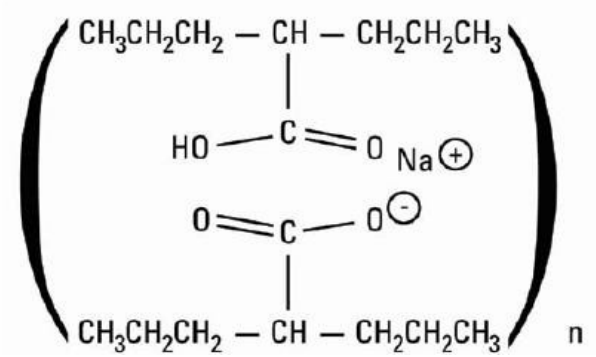
Section 1. Identification

Identification of the product

Product name: **Divalproex Sodium Delayed-Release Tablets USP**

Formula: $(C_{16}H_{31}NaO_4)_n$

Chemical Name: Sodium hydrogen bis (2-propylpentanoate)



Manufacturer / supplier identification

Company: **Cadila Healthcare Ltd. Ahmedabad, India**

Address: Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210. State: Gujarat. India

Contact for information: Tel.: +91 79 6868100 Fax: +91 79 3750319

Emergency Telephone No. Tel.: +91 79 6868100

Recommended use / Therapeutic Category Antimanic Agent, Anticonvulsant, GABA Agent.

Restriction on Use / Contraindications:	Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic dysfunction. Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug. Divalproex sodium is contraindicated in patients with known Urea cycle disorder.

Section 2. Hazard(s) Information

Dose and Administration	**For Mania:** lntial Dose- 750 mg daily, which should be gradually increased to achieve ·lowest therapeutic clinical dose which produces clinical effect. **For Epilepsy:** Monotherapy and Adjunctive Therapy in complex partial seizures in adults & pediatric patients down the age of 10 years & in simple and complex absence seizures. **Monotherapy:** 10 to 15 mg/kg/day, gradually increased by 5 to 10 mg/kg/week **Adjunctive Therapy:** 10 to 15 mg/kg/day, gradually increased by 5 to 10 mg/kg/week **Simple & Complex Absence Seizures:** 15 mg/kg/day, gradually increased by 5 to 10 mg/kg/day until seizures are controlled.
Adverse Effects	**Mania:** Nausea, Somnolence, Dizziness, Vomiting, Asthenia, Abdominal Pain, Dyspepsia, Rash **Migraine:** **Gastrointestinal System :** Nausea, Dyspepsia, Diarrhea, Vomitin, Abdominal Pain, Increased Apetite. **Nervous System :** Asthenia, Somnolence, Dizziness, Tremor Others:- Weight Gain, Back Pain, Alopecia. Epilepsy. **Body as a whole:** Headache, Asthenia, Fever. **Gastrointestinal System:** Nausea, Vomiting, Abdominal Pain, Diarrhea, Anorexia, Dyspepsia, Constipation. **Nervous System:** Somnolence, Tremor, Dizziness, Diplopia, Blurred Vision, Ataxia, Nystamus, Thinking abnormal, Amnesia. **Respiratory System:** Flu Syndrome,Infection, Bronchitis, Rhinitis. **Others:** Alopecia, Weight Loss.
Over Dose Effect	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 meg/mi.

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 overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

Medical Conditions

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 with Known or Suspected Mitochondrial Disease

Divalproex sodium is contraindicated in patients known to have 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 neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (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.

Contraindications

Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic dysfunction.
Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.
Divalproex sodium is contraindicated in patients with known Urea cycle disorder.

Pregnancy Category

Valproate can produce teratogenic effects. Data suggest that there is an increased incidence of congenital malformations associated with the puse of valproate by women with seizure disorders during pregnancy when compared to the incidence in women with seizure disorders who do not use antiepileptic drugs during pregnancy, the incidence in women with seizure disorders who use other antiepileptic drugs, and the background

Incidence For The general population. Therefore, valproate should be considered for women of child bearing potential only after the risks have been thoroughly discussed with the patient and weighed against The potential benefits of treatment.

There are multiple reports in the clinical literature that indicate the use of antiepileptic drugs during pregnancy results in an increased incidence of congenital malformations in offspring. antiepileptic drugs, including valproate, should be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their medical condition.

Pregnancy Category **Pregnancy Category D** for epilepsy and for manic episodes associated with bipolar disorder.
Pregnancy Category X for prophylaxis of migraine headaches.

Section 3. Composition / information on ingredients

Component	Exposure Limit	CAS No.
Principle Component :		
Divalproex sodium 125,250 & 500mg	Not Found	76584-70-8
Inactive Ingredients :		
Colloidal silicon dioxide	Not Found	7631-86-9
Corn starch	Not Found	523-577
hypermellose	Not Found	NA
Magnesium stearate	Not Found	577-04-0
Methacrylic acid copolymer dispersion	Not Found	79-41-4
Microcrystalline Cellulose	Not Found	9004-34-6
Polyethylene glycol	Not Found	25322-68-3
Sodium starch glycolate	Not Found	NA
Talc	Not Found	14807-96-6
Triethyl citrate	Not Found	NA
Povidone	Not Found	9003-39-8

Section 4. First - aid measures

General Remove from exposure. Remove contiminated Clothing. Person developing

serious hypersensitivity reaction must receive medical attention.

Overdose Treatment	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.

Section 5. Fire - fighting measures

Flash point	Not Found	**Upper Flammable Limit:**	Not Found
Auto-Ignition Temperature:	Not Found	**Lower Flammable Limit:**	Not Found
Extinguishing Media	Water Spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and material.	**Fire and Explosion Hazard**	This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with the dry material to dissipate the potential build-up of static electricity.

Fire Fighting Procedure	As with all fires, evacuate personnel to a safe area. Fire fighter should use self- contained breathing equipment and protective clothing.

Section 6. Accidental Release Measures

Spill Response	Wear approved respiratory protection, chemically compatible gloves and protective clothing. Wipe up spillage or collect spillage using high efficiency vacuum cleaner. Avoid breathing dust. Place spillage in appropriately labelled container for disposal. Wash spill site.

Section 7. Handling and Storage

Storage	Store at 20° to 25°C (68° to 77°F)**.** Dispense in a tight, light-resistant container.
Incompatibilities:	No Data available.

Section 8. Exposure controls / personal protection

Respiratory Protection	Protection from inhalation is not normally necessary. If ventilation is inadequate or dust is likely to generate, use of suitable dust mask would be appropriate.
Skin Protection	Skin protection is not normally necessary, however it is good practice to avoid contact with chemical to use suitable gloves when handling.
Eye protection	Eye protection is not normally necessary. If concerned wear protective goggles or

	glasses. Wash hands prior to touching eye and in particular handling contact lenses.
Protective Clothing	Protective clothing is not normally necessary, however it is good practice to use apron.

Section 9. Physical and chemical properties

Appearance

Divalproex Sodium Delayed-release Tablets, USP equivalent to 125 mg of valproic acid, are white to off-white having mottled spots, oval shaped, enteric-coated tablets with the logo of "ZA08" on one side and plain on other side.

Divalproex Sodium Delayed-release Tablets, USP equivalent to 250 mg of valproic acid, are white to off-white having mottled spots, oval shape, convex, enteric-coated tablets imprinted with the logo of "ZA07" on one side and plain on other side.

Divalproex Sodium Delayed-release Tablets, USP equivalent to 500 mg of valproic acid, are white to off-white having mottled spots, oval shape, beveled edge, convex enteric-coated tablets imprinted with the logo of "ZA06" on one side and plain on other side.

Solubility in water	Soluble in ethanol (95%), methanol, IPA & partially soluble in ether & water.	**Odour**	Characterised Odour
Boiling point	No Data Available	**Melting Point**	222°C
Evaporation rate	No Data Available	**Vapour density**	No Data Available
Reactivity in water	No Data Available	**Evaporation rate**	No Data Available
% Volatile by volume	No Data Available	**Specific gravity**	No Data Available
		Vapour pressure	No Data Available

Other information

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.

Section 10. Stability and Reactivity

Condition to avoid	Avoid exposure to extreme heat, light and moisture.	**Stable**	Stable under normal ambient and anticipated storage and handling conditions.

Decomposition Products	No Data Available	**Hazardous Reaction**	No data available.
Incompatibilities:	No Data Available		

Section 11. Toxicological information

General

Handling of formulated product is not expected to cause any toxicological affects. The data pertains to the ingredient in formulations, rather than this specie formulation.

Target organ

Eye contact, Skin contact and inhalation is not great risk as this product is tablet.

Other

HEPATOTOXICITY:
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When Divalproex sodium Delayed-Release Tablets are 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.

These incident usually have occurred during the first six months of treatment serious of fetal 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 appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months.

TERATOGENICITY:
Valproate can produce teratogenic effects such as Neural Tube defects (E.G., Spina Bifida). Accordingly, the use of Divalproex Sodium Delayed-Release Tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (E.G., Migraine) is contemplated.

A PATIENT INFORMATION LEAFLETDESCRIBING THE TERATOGENIC POTENTIAL OF V ALPROATE IS AVAILABLE FOR PATIENTS.

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 a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well As after several years of use. Patients and

guardians should be warned that abdominal pain, Nausea, Vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.

Section 12. Ecological information

Do not allow product to enter drinking water supplies, waste water or soil

Section 13. Disposal Consideration

Dispose the waste in accordance with all applicable Federal, State and local laws.

Section 14. Transport Information

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

Section 15. Regulatory Information

Generic Medicine. Approved by USFDA & the ANDA Number is 77100

Section 16. Other information

None

Date of issue: 28/05/2015 **Supersedes edition of:** 01

The information contained herein is based on the state of our knowledge. It Characterises the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.