1. Name of the medicinal Product

Gastro-Resistant Sodium Valproate Tablets BP 200 mg (VALPIN-200)

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Each tablet contains 200 mg of Sodium Valproate BP

2.2 Quantitative declaration

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solid Oral Dosage form, Tablets.

Distribution Category: POM.

White coloured, round shaped, biconvex, plain on both sides of enteric coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

For oral administration in the treatment of generalized, partial or other epilepsy.

4.2 Posology and Method of Administration

Route of administration: Oral. It should preferably be taken with or after food or as directed by physician. The tablets should be swallowed whole and not crushed or chewed. Daily dosage requirements vary according to age and body weight. The tablets may be given twice daily.

Dosage:

Adults: Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000-2000 mg per day, i.e. 20-30mg/kg/day body weight which may be further increased to 2500mg per day.

Children over 20kg:

Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day which may be increased to 35mg/kg body weight per day

Children under 20 kg:

20 mg/kg of body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Elderly: Although the pharmacokinetics of sodium valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control.

In patients with renal insufficiency: It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

In patients with hepatic insufficiency: salicylates should not be used concomitantly.

Female children and women of child bearing potential: It must be initiated and supervised by a specialist experienced in the management of epilepsy. It should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. It is prescribed and dispensed according to the valproate pregnancy prevention programme the benefits and risks should be carefully reconsidered at regular treatment reviews. It should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses.

Combined Therapy: When starting sodium valproate in patients already on other anti-consultant, these should be tapered slowly initiation of sodium valproate therapy should then be gradual, with target dose being reached after about 2 weeks.

NB: In children requiring doses higher than 40 mg/kg/day clinical chemistry and hematological parameters should be monitored. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary.

Salicylates should not be used in children under 16 years on (Reye's syndrome). In addition, in conjunction with sodium valproate, concomitant use in children under 3 years can increase the risk of liver toxicity.

4.3 Contraindications

It is contraindicated in the following situations: In pregnancy unless there is no suitable alternative treatment, in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled, active liver disease. Personal or family history of severe hepatic dysfunction, especially drug related. Patients with known urea cycle disorders hypersensitivity to sodium valproate, porphyria, and valproate is contraindicated in patients. Alpers-Huttenlocher Syndrome known to have mitochondrial disorders.

4.4 Special Warnings and Special Precautions for Use

Although there is no specific evidence of sudden recurrence of underlying symptoms for withdrawal of sodium valproate. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms.

It advised by health professionals, the generic switching of valproate preparations is not normally recommended due to the implications of possible variations in plasma concentrations.

Patient should take special cautions: Liver dysfunction: Severe liver damage, including hepatic failure sometimes very rarely suggestive signs, on specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain. Detection: It should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease. Pancreatitis: which may be severe and result in very rarely may report serious effect.

Female children, women of childbearing potential and pregnant women: pregnancy prevention programme: It is contraindicated in the pregnancy and in women of childbearing potential.

Conditions: The prescriber must ensure that: Female children: The parents/caregivers of female children understand the need to contact the specialist once. Pregnancy planning: Pregnancy must be excluded before start of treatment with sodium valproate with the result of a pregnancy test confirmed by your physician.

Contraception: patients must use an effective method of birth control (contraception) during your entire treatment. Oestrogen-containing products may lower valproate levels in your blood.

Aggravated convulsions: An increase in the number and severity of convulsions. The patients should be advised to consult their physician immediately.

Patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Caregivers of patients should be advised to physician, should signs of suicidal ideation or behaviour emerge. The concomitant use of valproate and carbapenem agents is not recommended. Patients with known or suspected mitochondrial disease.

Patient should take precautions:

Hematological tests, renal insufficiency: Blood tests may wish to do blood tests before you start the treatment and during your treatment. Renal function test should be performed. Patients with systemic lupus erythematosus.

Urea cycle disorders where too much ammonia builds up in the body hyperammonaemia with sodium valproate.

Weight gain: very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it.

Diabetic patients: It is eliminated mainly through the kidneys, partly in the form of ketone bodies this may give false positives in the urine testing of possible diabetics.

Patients with an underlying carnitine palmitoyl transferase type II deficiency should be warned of the greater risk of rhabdomyolysis when taking Sodium valproate.

Alcohol: Alcohol intake is not recommended during treatment with valproate.

Pregnancy: It is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. It should not be used during

pregnancy and women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

Lactation: It is excreted in breast milk in small amount 1-10% serum concentration. It is not known what effect this would have on a nursing infant. Therefore, it should not recommended while lactation.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products and other forms of interaction effects of sodium valproate on other drugs: antipsychotics, MAO inhibitors, antidepressants and benzodiazepines may potentiate the effect (olanzapine, primidone, phenytoin, lamotrigine, propofol, zidovudine, nimodipine, temozolomide)

Effects of other drugs on sodium valproate: Anti-epileptics drugs: phenytoin, anti-malarial agents: mefloquine and chloroquine, vitamin K-dependent factor anticoagulants, carbapenem antibiotics (such as panipenem, meropenem), rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

Protease inhibitors: protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered.

Cholestyramine: it may lead to a decrease in plasma level of valproate when co-administered. Oestrogen-containing products, including hormonal contraceptives, concomitant use of valproate and topiramate or acetazolamide has been associated with encephalopathy and hyperammonaemia.

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

4.6 Pregnancy and Lactation

Pregnancy: It is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. It should not be used during pregnancy and women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

Lactation: It is excreted in breast milk in small amount 1-10% serum concentration. It is not known what effect this would have on a nursing infant. Therefore, it should not have recommended while lactation.

4.7 Effects on ability to Drive and use Machines

Not Applicable

4.8 Undesirable Effects

Very common: Nausea, tremor.

Common: Vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhea, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, confusional state, hallucinations, aggression, agitation, disturbance in attention, hyponatraemia, weight increased, dysmenorrhea, haemorrhage, deafness, a cause and effect relationship has not been established, urinary incontinence.

Uncommon: Pancreatitis, sometimes lethal, coma, encephalopathy, lethargy, reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions, angioedema, rash, hair disorder (such as abnormal hair growth and texture, hair colour changes), amenorrhea, vasculitis, renal failure, hypothermia, non-severe peripheral oedema, pleural effusion.

Rare: Reversible dementia associated with reversible cerebral atrophy, cognitive disorder, cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions reported, abnormal behaviour, psychomotor hyperactivity, learning disorder, hyperammonaemia, obesity, hypothyroidism, bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, male infertility, polycystic ovaries, diplopia, enuresis, tubulointerstitial nephritis, reversible falconi syndrome, systemic lupus erythematosus, rhabdomyolysis, coagulation factors decreased, myelodysplastic syndrome.

Very rarely: Encephalopathy and coma observed, gynaecomastia occurred. Risk in the neonate cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy.

4.9 Overdose

In event of overdose is unlikely to occur and not reported. Symptoms: There are unlikely to be any symptoms other than nausea, vomiting and dizziness. Signs of acute massive overdose, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. Symptoms may however be variable and seizures may occur in the presence of very high plasma levels. The presence of sodium content in the sodium valproate formulations may lead to hypernatraemia when taken in overdose. Symptomatic therapy is recommended: Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Haemodialysis and haemoperfusion have been used successfully, naloxone successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

The most likely mode of action of sodium valproate is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

5.2 Pharmacokinetic Properties

The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/L (278 -694 µmol/L). Distribution: The percentage of free (unbound) drug is usually between 6-15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range. The therapeutic effects of sodium valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels. In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at

delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers. Metabolism: Sodium valproate metabolized through major pathway of valproate biotransformation is glucuronidation (~40%), mainly via UGT1A6, UGT1A9 andUGT2B7. Elimination: The half-life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children. Interaction with oestrogen-containing products Inter-individual variability has been noted. Sodium valproate is eliminated mainly through the kidneys.

5.3 Preclinical Safety Data

Not Applicable

6. Pharmaceutical Particulars

6.1 List of Excipients

Colloidal Anhydrous Silica
Microcrystalline Cellulose (PH 102)
Croscarmellose Sodium
Hydroxy Propyl Cellulose
Methanol
Purified Talc
Magnesium Stearate
Isopropyl Alcohol
Dichloromethane (Methylene Chloride)
Insta Moistshield (A21R01256):
HPMC 2910/Hypromellose
Diethyl Phthalate
Ethyl Cellulose
Talc
Titanium Dioxide
Instacoat EN HPMC
Hypromellose Phthalate

Diethyl Phthalate

Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C, Store in a dry place. Protect from light and moisture.

6.5 Nature and Contents of Container

10 Tablets are packed in Alu-Strip pack. Such 10 Strips are packed in a printed carton with packing insert.

6.6 Special precaution for disposal and other handling

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

7. Marketing Authorization Holder and Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Tal.-Kalol,
Dist.- Gandhinagar, Gujarat State, India.
Telephone no.: +91-079-41078096
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited

Trimul Estate, Khatraj, Tal.-Kalol,
Dist.- Gandhinagar, Gujarat State, India.
Telephone no.: +91-079-41078096
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number

To be included after obtaining first registration.

9. Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

10. Date of Revision of the Text

July, 2023

11. Dosimetry (If Applicable)

Not Applicable

12. Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable