For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Abridged Prescribing Information
VALPARIN ® CHRONO / ALKALETS / SYRUP

COMPOSITION :
Sodium Valproate Gastro-Resistant Tablets I.P.
VALPARIN® 200 ALKALETS – Each enteric coated tablet contains Sodium Valproate I.P. 200mg
VALPARIN® 500 ALKALETS – Each enteric coated tablet contains Sodium Valproate I.P. 500mg

Controlled Release Tablets of Sodium Valproate and Valproic Acid
VALPARIN® CHRONO 200 - Sodium Valproate I.P. 133mg + Valproic Acid I.P. 58mg
VALPARIN® CHRONO 300 - Sodium Valproate I.P. 200mg + Valproic Acid I.P. 87mg
VALPARIN® CHRONO 500 - Sodium Valproate I.P. 333mg + Valproic Acid I.P. 145mg

Sodium Valproate Oral Solution I.P.
VALPARIN® 200 – Sodium Valproate I.P. 200mg/5ml

THERAPEUTIC INDICATIONS: (1) treatment of generalized or partial epilepsy, particularly with the following patterns of seizures: absence, myoclonic, tonic-clonic, atonic, mixed, as well as for partial epilepsy: simple or complex seizures, secondary generalized seizures, specific syndromes (West, Lennox-Gastaut). (2) treatment of manic episodes associated with bipolar disorders.

DOSAGE AND ADMINISTRATION: *For seizure control*: Initial daily dosage 10-15mg/kg, then titrated up to 20-30mg/kg. Careful monitoring required when receiving daily doses higher than 50mg/kg. Valparin Chrono allows once daily dosing. *For treating mania* Initially dosage 600mg daily increasing by 200mg/day at three-day intervals (Range: 1000 to 2000mg /day). When control is not achieved dose may be further increased to 2500mg/day. *Use in Children*: Epilepsy indication - Oral solution is more appropriate for children less than 11 years. Only for Bipolar indication – In children and adolescents the efficacy of valparin for the treatment of manic episodes in bipolar disorder has not beenestablished in patients aged less than18 years. Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.

SAFETY-RELATED INFORMATION: Contraindications: For treatment of epilepsy and biploar disorder contraindicated in pregnancy unless there is no suitable alternative treatment, in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled. For all indications: Hypersensitivity to sodium valproate or valproic acid. Acute and chronic hepatitis; Patient or family history of severe hepatitis, especially drug related; Hepatic porphyria; Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ and in children under two years of age who are suspected of having a POLG-related disorder; Patients with known disorders. Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see "Precautions" Patients at risk of hypocarnitinemia).

WARNINGS/PRECAUTIONS: Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations, neurodevelopmental disorders and Lower weight at birth for the gestational age from in utero exposure. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. Severe liver damage resulting sometimes in fatalities has exceptionally been reported, severe pancreatitis which may result in fatalities has been very rarely reported. Monitoring of signs and symptoms of ototoxicity is recommended. *In utero* exposure to valproate may result in eye malformations (including colobomas, microphthalmos). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision. *Estrogen-containing products:* Valproate does not reduce efficacy of hormonal contraceptives: However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products. *Severe Cutaneous Adverse Reactions (SCARS) and Angioedema:* SCARs such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and angioedema, have been reported in association with valproate treatment. If diagnosis of SCARs or angioedema is confirmed, then valproate treatment must be discontinued. *Suicidal ideation and behavior*: Patients should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. *Carbapenem agents*: Concomitant use of valproate and carbapenem agents is not recommended. *Patients with known or suspected mitochondrial disease:* Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations or mitochondrial DNA as well as the nuclear-encoded POLG gene. *Aggravated convulsions:* As with other antiepileptic drugs, some patients may experience, instead of an

improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately. *Metamizole*: Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy.. *Methotrexate:* Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Liver function tests should be carried out before therapy, and periodically during the first 6 months especially in patients at risk. Blood tests are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding. Potential benefit should be weighed against its potential risk in patients with systemic lupus erythematosus. When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate. Patients should be warned of the risk of weight gain at initiation and appropriate strategies should be adopted to minimize the risk. Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Alcohol intake is not recommended during treatment. Monotherapy is recommended in children under the age of 3 years. Concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters. Patients with renal insufficiency should be closely monitored, it may be necessary to decrease the dosage. An increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam was indicated in a retrospective observational study. Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually.
Pregnancy: Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled. **Neurodevelopmental disorders from *in utero* exposure:** Data have shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers. **Lactation:** Excretion of valproate in breast milk is low with a concentration of 1% to 10% of maternal serum levels. Based on literature breastfeeding can be envisaged considering the valproate safety profile especially hematological disorders**.**

ADVERSE REACTIONS: Very common (≥10%): tremor, nausea, Common (≥1% and<10%) : anaemia, thrombocytopenia, extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus, dizziness, deafness, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea, urinary incontinence, hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders, hyponatraemia, weight increased, haemorrhage, liver injury, dysmenorrhea, confusional state, hallucinations, aggression, agitation, disturbance in attention. *Pediatric population*- Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see section *Precautions*) or degenerative disease. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age. Psychiatric disorders such as abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

For full prescribing information, refer to the company website www.sanofi.in

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