Depakine ® Abridged Prescribing Information:

1. NAME & PRESENTATION: Depakine Chrono 500 mg prolonged-release scored film-coated tablets, each tablet contains Sodium valproate 333.00 mg, Valproic acid 145.00 mg and Amount equivalent to sodium valproate 500.00 mg

2. Therapeutic INDICATIONS:

In adults: either as single-agent therapy, or in combination with another antiepileptic treatment:

Treatment of generalised epilepsy: clonic, tonic, tonic-clonic, absence, myoclonic and atonic seizures, and Lennox-Gastaut syndrome.

Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

In children: either as single-agent therapy, or in combination with another antiepileptic treatment:

Treatment of generalised epilepsy: clonic, tonic, tonic-clonic, absence, myoclonic and atonic seizures, and Lennox-Gastaut syndrome.

Treatment of partial epilepsy: partial seizures with or without secondary generalisation

3. DOSAGE & POSOLOGY OF ADMINISTRATION: Posology

The initial daily dose is usually 10 to 15 mg/kg, after which doses are increased up to the optimal dose (see Initiation of treatment).

The mean dose is 20 to 30 mg/kg per day. However, if seizures are not brought under control at this dose, the dose may be increased and patients must be closely monitored.

In children, the usual dose is 30 mg/kg per day.

In adults, the usual dose is 20 to 30 mg/kg per day.

In elderly patients, the dose should be determined based on the control of seizures.

The daily dose should be determined based on age and bodyweight; however, the significant variations in inter-individual sensitivity to valproate must be taken into account.

No clear correlation between daily dose, serum levels and therapeutic effect has been established: the dosage should be determined mainly on the basis of clinical response.

Determination of plasma valproic acid levels should be considered along with clinical monitoring when control of seizures is not achieved or when adverse effects are suspected. The effective therapeutic range is usually between 40 and 100 mg/L (300 to 700 micromol/L).

Method of administration

Oral route.

The medicinal product should be administered daily as 1 or 2 divided doses, preferably during meals. Administration as a single daily dose is possible in well-controlled epilepsy.

Swallow the tablet whole without crushing or chewing.

Initiation of treatment

In patients in whom appropriate control has been obtained with immediate-release forms of Depakine, it is recommended that the daily dose be maintained when replacing treatment with Depakine Chrono.

If the patient is already being treated and is taking other antiepileptics, treatment with Depakine Chrono should be initiated gradually, to reach the optimal dose in approximately 2 weeks, then the concomitant treatments reduced if necessary on the basis of treatment efficacy.

If the patient is not taking any other antiepileptics, the dosage should preferably be increased step-wise every 2 or 3 days, in order to reach the optimal dose in approximately 1 week.

If necessary, combination treatment with other antiepileptics should be instituted gradually**4. SPECIAL POPULATION:** Renal impairment Due to the hydrochlorothiazide component, CoAprovel is not recommended for patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. No dosage adjustment is necessary in patients with renal impairment whose renal creatinine clearance is ≥ 30 ml/min. Hepatic impairment CoAprovel is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function. No dosage adjustment of CoAprovel is necessary in patients with mild to moderate hepatic impairment

4. CONTRA-INDICATIONS: Pregnancy unless there is no suitable alternative treatment (Women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled. History of hypersensitivity to valproate, valproate semi sodium, valpromide or to any of the excipients. Acute hepatitis. Chronic hepatitis. Patient or family history of severe hepatitis, especially drug related. Hepatic porphyria. Patients with known urea cycle disorders. Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase gamma (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under 2 years of age who are suspected of having a POLG-related disorder. Combination with St John's Wort

WARNINGS & PRECAUTIONS: Pregnancy Prevention Program Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neuro-developmental disorders (see section 4.6). Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated. If no other treatment is possible, the Pregnancy Prevention Program below must be complied with. Depakine is contraindicated in the following situations:

• In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).

• In women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilledimpairment (creatinine clearance ≥ 30 ml/min but < 60 ml/min) this fixed dose combination should be administered with caution.

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate-exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that the Patient Card is provided with every valproate dispensing and that the patients understand its content and the patients are advised not to stop valproate medication

6. INTERACTIONS: There is a risk of decreased plasma concentrations and reduced efficacy of the antiepileptic. With St. John's Wort, Lamotrigine, There is a risk of seizures due to a rapid decrease in valproic acid plasma concentrations, which may become undetectable**.** There is a risk of seizures due to a rapid decrease in valproic acid plasma concentrations, which may become undetectable with Penems, Acetazolamide, Oestrogen-containing products, including oestrogen-containing hormonal contraceptives are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase valproate clearance, which in turn is thought to cause a decrease in serum valproate concentrations and

7. PREGNANCY AND LACTATION: Valproate is contraindicated during pregnancy unless there is no suitable alternative treatment and in women of childbearing potential, unless the conditions of the Pregnancy Prevention Program are fulfilled. Both valproate monotherapy and valproate polytherapy including other antiepileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy. Valproate was shown to cross the placental barrier both in animal species and in humans. Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Haematological disorders have been shown in breast-fed newborns/infants of treated women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Depakine therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

8. EFFECTS ON ABILITY TO DRIVE: The attention of patients, particularly those who drive or use machines, must be drawn to the risk of drowsiness, especially in patients receiving anticonvulsant polytherapy or concomitant administration with other medicinal products that may increase drowsiness.

9. ADVERSE REACTIONS: Congenital, familial and genetic disorders Congenital malformations and neuro-developmental disorders. Blood and lymphatic system disorder Common: anemia, thrombocytopenia. Cases of dose-dependent thrombocytopenia have been reported, generally discovered systematically and without any clinical repercussions. In patients with asymptomatic thrombocytopenia, if possible, given the platelet level and control of the disease, simply reducing the dose of this medicinal product usually leads to resolution of thrombocytopenia. Uncommon: leukopenia, pancytopenia. Rare: bone marrow aplasia or pure red cell aplasia, agranulocytosis, macrocytic anemia, macrocytosis. Renal and urinary disorders Common: urinary incontinence Uncommon: renal failure. Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome.

10.Overdose: Signs of acute massive overdose usually include a calm coma, which may be more or less deep, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock. A few cases of intracranial hypertension related to cerebral oedema have been described. Patient management in a hospital setting includes gastric lavage if indicated, maintenance of effective diuresis, cardiorespiratory monitoring. In very serious cases, extra-renal purification may be performed if necessary. The prognosis for such poisoning is generally favourable. However, a few deaths have been reported. The sodium content in valproate-containing medicinal products can lead to hypernatremia in the event of overdose.

11.Pharmacodynamics: Valproate is pharmacologically active primarily on the central nervous system. The drug has an anticonvulsant effect on a very wide range of seizures in animals and epilepsy in humans. Experimental and clinical studies on valproate suggest 2 types of anticonvulsant effect. The first is a direct pharmacological effect related to valproate concentrations in the plasma and the brain. The second appears to be indirect and is probably related to the metabolites of valproate, which remain in the brain, or to changes in neurotransmitters or direct membrane effects. The most widely accepted hypothesis is that of gamma-aminobutyric acid (GABA) levels, which increase following valproate administration. Valproate reduces the duration of intermediate stages of sleep, with a concomitant increase in slow sleep.

12. MARKETING AUTHORIZATION HOLDER: SANOFI-AVENTIS FRANCE 82, AVENUE RASPAIL94250 GENTILLY, FRANCE
Abbreviated Prescribing Information based on the EU SmPC as of March 2015. Always refer to the full Summary of Product Characteristics (SmPC) before prescribing.