**Depakine ® Abridged Prescribing Information:**

**1. NAME & PRESENTATION**: Depakine® 400 mg/4 mL injection for IV , Each Pack contains 400 mg of Sodium Valproate per 4 ml reconstitution.

**2. Therapeutic INDICATIONS**:

Temporary treatment of epilepsy in adults and children, as a replacement for the oral form when the oral form cannot be used temporarily.

**3. DOSAGE & POSOLOGY OF ADMINISTRATION**:

after the last oral dose, intravenous administration of sodium valproate in a 0.9% sodium chloride solution for injection:

• either as a continuous infusion over 24 hours,

• or divided into 4 one-hour infusions per day, at the previous dosage (mean usual dosage: 20 to 30 mg/kg/day).

When effective plasma concentrations must be reached rapidly and maintained: intravenous injection over 5 minutes of a 15 mg/kg bolus; then follow on with a continuous infusion, at a flow rate of 1 mg/kg/hour to be gradually adjusted in order to reach blood valproic acid levels of approximately 75 mg/l. Then adjust the flow rate depending on the clinical course.

As soon as the infusion is stopped, reinitiation of treatment with the oral form will immediately compensate for the amount of drug eliminated. This will be carried out either at the previous dose or after dose adjustment**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 France82 avenue Raspail 94250 Gentilly – France. Abbreviated Prescribing Information based on the EU SmPC as of April 2020. Always refer to the full Summary of Product Characteristics (SmPC) before prescribing.