SUMMARY OF PRODUCT CHARACTERISTICS

Vilapro® 57.64 mg/ml Syrup

1. NAME OF THE MEDICINAL PRODUCT

Vilapro® 57.64 mg/ml Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Vilapro® syrup contains 57.64 mg sodium valproate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

Vilapro® syrup is clear, yellowish oral solution, available in 150 ml amber glass bottle.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

- Treatment of generalized epilepsy: clonic, tonic, tonic-clonic, absence, myoclonic and atonic seizures, and Lennox-Gastaut syndrome.
- Treatment of partial epilepsy: partial seizures with or without secondary generalization.

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

- Treatment of generalized epilepsy: clonic, tonic, tonic-clonic, absence, myoclonic and atonic seizures, and Lennox-Gastaut syndrome.
- Treatment of partial epilepsy: partial seizures with or without secondary generalization.

In children:

- Prevention of recurrence of seizures after one or more febrile convulsions that meet the criteria for complicated febrile convulsions, when intermittent benzodiazepine prophylaxis has failed.

Prescription only medicine.

4.2. Posology and method of administration

Female children, female adolescents, women of childbearing potential and pregnant women

Vilapro® syrup should be initiated and supervised by a specialist experienced in the management of epilepsy.

Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6)

and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Vilapro® syrup should be prescribed as monotherapy and at the lowest effective dose.

The daily dose should be divided into at least two single doses.

Of the oral pharmaceutical forms, the syrup and oral solution are particularly suitable for administration in children under 11 years of age.
Dosage Mean daily dose:
• Infants and children: 30 mg/kg (syrup and oral solution should preferably be used).
• Adolescents and adults: 20 to 30 mg/kg (prolonged-release tablets should preferably be used).
The medicinal product should be prescribed only in milligrams.
The bottle of syrup is supplied with a spoon.

Method of administration Oral use.
The syrup should only be administered using the spoon supplied in the box. The daily dose should preferably be administered during meals:
• as 2 divided doses in patients under 1 year of age,
• as 3 divided doses in patients over 1 year of age. Initiation of treatment:
• If the patient is already being treated and is taking other antiepileptics, treatment with sodium valproate should be initiated gradually, to reach the optimal dose in approximately two weeks, then the concomitant treatments reduced if necessary on the basis of treatment efficacy.
• If the patient is not taking any other antiepileptics, the dose should preferably be increased step-wise every 2 or 3 days, in order to reach the optimal dose in approximately one week.
• If necessary, combination treatment with other antiepileptics should be instituted gradually (see section 4.5).

4.3. Contraindications

• Hypersensitivity to valproate, valproate semisodium, valpromide or any of the excipients listed in section 6.1.
• Acute hepatitis.
• Chronic hepatitis.
• Personal or family history of severe hepatitis, particularly drug-related.
• Hepatic porphyria.
• Patients with known urea cycle disorders (see section 4.4).
• Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase Y (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
• Combination with St. John's Wort (see section 4.5).

4.4. Special warnings and precautions for use

Female Children/Female adolescents/Women of childbearing potential/Pregnancy
Valproate should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of neuro-developmental disorders in infants exposed *in utero* to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Valproate plans a pregnancy or if she becomes pregnant. Women of childbearing potential must use effective contraception during treatment and be completely informed of the risks associated with the use of Valproate during pregnancy (see section 4.6). The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks. He or she must also ensure that the patient has duly filled in and signed the treatment agreement form. In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of neuro-developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6). Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.

Exacerbation of seizures As with other antiepileptics, administration of valproate may, instead of improvement, lead to a reversible exacerbation of seizure frequency and severity (including status epilepticus), or the onset of a new type of seizure. Patients should be advised to consult their physician immediately if exacerbation of seizures occurs (see section 4.8). These seizures should be differentiated from those that may occur due to a pharmacokinetic interaction (see section 4.5), toxicity (liver disease or encephalopathy - see sections 4.4 and 4.8) or overdose. Since this medicinal product is metabolized into valproic acid, it should not be combined with other medicinal products undergoing the same transformation to avoid an overdose of valproic acid (e.g. valproate semisodium, valpromide).

Liver disease

Conditions of onset Exceptional cases of liver damage with a severe or sometimes fatal outcome have been reported. Infants and young children under the age of 3 with severe epilepsy and, in particular, epilepsy associated with brain damage, mental retardation and/or a genetic metabolic or degenerative disease are the most at risk. Over the age of 3, the incidence of onset is significantly reduced and gradually decreases with age. In the great majority of cases, such liver damage has been observed within the first 6

months of treatment, usually between the 2nd and 12th week and generally during multiple-agent antiepileptic treatment.

Warning signs Early diagnosis is based above all on clinical findings. It is particularly important to take into consideration, and especially in high-risk patients (see Conditions of onset), two types of manifestations which may precede jaundice:

- firstly, non-specific systemic signs, generally of sudden onset, such as asthenia, anorexia, exhaustion, drowsiness, sometimes accompanied by repeated vomiting and abdominal pain,
- secondly, a recurrence of epileptic seizures despite proper treatment compliance.

Patients, or their families if the patient is a child, should be advised to consult their physician immediately if these symptoms occur. In addition to a physical examination, liver function tests should immediately be performed.

Detection During the first 6 months of treatment, liver function should be monitored periodically.

The most pertinent of the conventional tests are those reflecting protein synthesis and, in particular, PT (prothrombin time). Confirmation of abnormally low PT values, especially if there are also other abnormal laboratory findings (significant reduction in fibrinogen and coagulation factors, elevated bilirubin, elevated transaminase levels - see section 4.4), should lead to discontinuation of treatment (and, as a precaution, discontinuation of salicylate derivatives if they are concomitantly prescribed, since they use the same metabolic pathway).

Pancreatitis Pancreatitis with a sometimes fatal outcome has very rarely been reported. This can be observed irrespective of age and treatment duration, with young children appearing to be particularly at risk. Pancreatitis with an unfavorable outcome is generally observed in young children or in patients with severe epilepsy, brain damage or those taking multiple-agent antiepileptic treatment. If pancreatitis occurs along with liver failure, the risk of fatal outcome is increased. In the event of acute abdominal pain or gastrointestinal signs such as nausea, vomiting and/or anorexia, a diagnosis of pancreatitis must be considered and, in patients with elevated pancreatic enzymes, treatment should be discontinued, and the necessary alternative therapeutic measures implemented.

Risk of suicide Suicidal ideation and behavior have been reported in patients treated with antiepileptics in several indications. A meta-analysis of data from randomized, placebo-controlled trials of antiepileptic drugs has also shown a slight increase in risk of suicidal ideation and behavior. The causes of this risk are unknown and the available data do not make it possible to rule out an increased risk with valproate. Consequently, patients must be closely monitored for any signs of suicidal ideation and behavior, and appropriate treatment should be considered. Patients (and their care providers) should be advised to seek medical advice if there are signs of suicidal ideation or behavior.

Patients with known or suspected mitochondrial disease Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear gene encoding the mitochondrial enzyme polymerase Y (POLG).In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the POLG gene, e.g. Alpers-Huttenlocher syndrome. POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or

complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3)
Interaction with other medicinal products Coadministration of this medicinal product with lamotrigine and penems is not recommended (see section 4.5). As this medicine contains sucrose and sorbitol, it is not recommended in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency (rare hereditary diseases). This medicinal product contains 13.8 mg of sodium per 100 mg of sodium valproate. This must be taken into account in patients following a strict low-sodium diet. This medicinal product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, that can cause allergic reactions (possibly delayed).
Precautions for use Liver function tests should be performed before starting treatment (see section 4.3) and then periodically for the first 6 months, particularly in patients at risk (see section 4.4). It should be emphasized that, as with most antiepileptics, an isolated and transient, moderate elevation in transaminase levels may be observed, without any clinical signs, particularly at the start of treatment. Should this occur, it is recommended that a more complete laboratory workup be performed (in particular, prothrombin time), that the dosage be re-evaluated if necessary, and that the tests be repeated based on changes in the parameters. In children under the age of 3, it is recommended that valproate only be used as single-agent treatment, after having weighed the therapeutic value against the risk of liver disease and pancreatitis in patients in this age group (see section 4.4). Blood tests (complete blood count including platelets, bleeding time and coagulation parameters) are recommended prior to treatment, then after 15 days and at the end of treatment, and also before any surgery, and in the event of hematomas or spontaneous bleeding (see section 4.8). In children, the simultaneous prescription of salicylate derivatives should be avoided, due to the risk of hepatotoxicity (see section 4.4) and the risk of bleeding. In patients with kidney failure, elevated circulating valproic acid concentrations in the blood should be taken into account and the dose reduced accordingly. This medicinal product is contraindicated in patients with urea cycle enzyme deficiencies. A few cases of hyperammonemia with stupor or coma have been described in these patients (see section 4.3). In children with a history of unexplained hepatic and gastrointestinal disorders (anorexia, vomiting, acute episodes of cytolysis), episodes of lethargy or coma, mental retardation or with a family history of neonatal or infant death, metabolic tests and, in particular, fasting and post-prandial blood ammonia tests must be performed prior to any valproate treatment. Although it is recognized that this medicinal product only causes immunological disturbances in exceptional cases, the benefit/risk ratio should be weighed in patients with systemic lupus erythematosus. When initiating treatment, the patient should be informed of the risk of weight gain and of the appropriate measures which are mainly dietary to be taken to minimize this effect. As valproate is excreted primarily in the urine, partly in the form of ketone bodies, tests for ketonuria may yield false positive results in patients with diabetes. Patients with carnitine palmitoyltransferase type II (CPT-II) deficiency must be warned of the increased risk of rhabdomyolysis associated with valproate use. Use of alcohol is not recommended throughout treatment with valproate.

Important information about some of the ingredients of Vilapro® syrup
This medicine contains:
Methyl parahydroxybenzoate and propyl parahydroxybenzoate: These may cause allergic reactions (possibly delayed).

Sucrose (Each 1ml contains 600 mg).
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Also this sucrose may be harmful to the teeth.

Sorbitol (Each 1ml contains 150 mg):
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5. Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

+ St. John's Wort
Risk of reduced plasma concentrations and decreased efficacy of the anticonvulsant.

Inadvisable combinations

+ Lamotrigine
Higher risk of serious skin reactions (toxic epidermal necrolysis).
Furthermore, an increase in lamotrigine plasma concentrations may occur (decreased hepatic metabolism by sodium valproate).
If coadministration proves necessary, close clinical monitoring is required.

+ Penems
Risk of seizures due to a rapid decrease in valproic acid plasma concentrations, which may become undetectable.

Combinations requiring precautions for use

+ Acetazolamide
Increased hyperammonemia with increased risk of encephalopathy. Regular monitoring of clinical and laboratory parameters.

+ Aztreonam
Risk of seizures due to a decrease in valproic acid plasma concentrations.
Clinical monitoring, plasma assays and possible dose adjustment of the anticonvulsant during treatment with the anti-infective agent and after its discontinuation.

+ Carbamazepine
Increased plasma concentrations of the active metabolite of carbamazepine with signs of overdose. In addition, reduced valproic acid plasma concentrations due to its increased hepatic metabolism by carbamazepine. Clinical monitoring, plasma assays and dose adjustment of both anticonvulsants.

+ Felbamate
Increased serum valproic acid concentrations with a risk of overdose.
Clinical monitoring and monitoring of laboratory parameters and possible valproate dose adjustment during treatment with felbamate and after its discontinuation.

+ Phenobarbital, and by extrapolation primidone
Increased hyperammonemia with increased risk of encephalopathy. Regular monitoring of clinical and laboratory parameters.
+ Phenytoin, and by extrapolation fosphenytoin
Increased hyperammonemia with increased risk of encephalopathy. Regular monitoring of clinical and laboratory parameters.
+ Propofol
Possible increase in propofol blood levels. When coadministered with valproate, a reduction in propofol dose should be considered.
+ Rifampicin
Risk of seizures due to increased hepatic metabolism of valproate by rifampicin. Clinical monitoring and monitoring of laboratory parameters and possible anticonvulsant dose adjustment during treatment with rifampicin and after its discontinuation.
+ Rufinamide
Possible increase in rufinamide concentrations, in particular in children weighing less than 30 kg.
In children weighing less than 30 kg: the total dose of 600 mg/day after dose titration should not be exceeded.
+ Topiramate
Increased hyperammonemia with increased risk of encephalopathy. Regular monitoring of clinical and laboratory parameters.
+ Zidovudine
Risk of increased adverse effects of zidovudine, particularly hematological effects, due to decrease in its metabolism by valproic acid. Regular monitoring of clinical and laboratory parameters. A blood count should be performed to test for anemia during the first two months of the combination.
+ Zonisamide
Increased hyperammonemia with increased risk of encephalopathy. Regular monitoring of clinical and laboratory parameters.
Combinations to be taken into account
+ Nimodipine (oral route and, by extrapolation, by injection)
Risk of enhanced hypotensive effect of nimodipine due to an increase in its plasma concentrations (decrease in its metabolism by valproic acid).
Other forms of interaction
+ Oral contraceptives
As valproate has no enzyme-inducing activity, it does not reduce the efficacy of estrogen-progestogen hormonal contraception in women.
+ Lithium
Valproate has no effect on blood lithium levels.

4.6. Fertility, pregnancy and lactation

Pregnancy

Valproate should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment.
In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and multiple-agent therapy including valproate are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic multiple-agent therapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) have shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose-dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations.

The most common types of malformations include neural tube closure defects (approximately 2 to 3%), facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects (in particular, hypospadias), limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Neuro-developmental disorders

Studies have shown that exposure to valproate *in utero* increases the risk of neuro-developmental disorders in exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The period of risk could involve the entire pregnancy. Studies in preschool children exposed *in utero* to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (aged 6) with a history of valproate exposure *in utero* was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate in utero that the decrease in IQ may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to valproate *in utero* are at increased risk of pervasive developmental disorders (autism spectrum disorders) (approximately three- fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data to date suggest that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children, female adolescents and women of childbearing potential (see above and section 4.4)

Valproate should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated. Women of childbearing potential must use effective contraception during treatment.

If a woman wants to plan a pregnancy or if she is pregnant:

- valproate therapy should be reassessed,
- all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible,
- a pre-conception consultation is recommended.

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in

the management of epilepsy. During pregnancy, maternal tonic-clonic seizures and status epilepticus with hypoxia may have serious consequences and even be fatal for the mother and the unborn child.
If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy (no alternative), it is recommended to:
• use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged-release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.
• provide folate supplementation before the pregnancy, which may decrease the risk of neural tube closure defects common to all pregnancies. However the available evidence does not suggest it prevents the malformations due to valproate exposure.
• institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Before delivery

Coagulation tests should be performed in the mother before delivery, including in particular a platelet count, fibrinogen levels and coagulation time (activated partial thromboplastin time: aPTT).

Risk in the neonate

• Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal.
However, this syndrome must be distinguished from the vitamin K factor deficiency induced by phenobarbital and enzymatic inducers. Normal hemostasis test results in the mother do not make it possible to rule out hemostasis abnormalities in the neonate. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates at birth.
• Cases of hypoglycemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
• Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
• Withdrawal syndrome (in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been observed in breast-fed newborns/infants of treated women (see section 4.8). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from valproate therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (in particular, decreased sperm motility) (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7. Effects on ability to drive and use machines

The attention of patients, particularly those who drive or use machines, must be drawn to the risk of drowsiness, especially in patients receiving multiple-agent anticonvulsant therapy or concomitant administration with other medicinal products that may increase drowsiness.

4.8. Undesirable effects

Classification of expected incidence rates:
Very common (≥ 10 %); Common (≥ 1 % - < 10 %); Uncommon (≥ 0.1 % - < 1 %); Rare (≥ 0.01 % - < 0.1 %); Very rare (< 0.01 %); Not known (cannot be estimated from the available data).

Congenital, familial and genetic disorders

• Congenital malformations and neuro-developmental disorders (see sections 4.4 and 4.6).

Blood and lymphatic system disorders

• 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.

Investigations

• Common: weight gain*,
• Rare: decrease in at least one coagulation factor, abnormal coagulation test results (such as increased prothrombin time, increased activated partial thromboplastin time, increased thrombin time, increased INR) (see sections 4.4 and 4.6), vitamin B8 (biotin) deficiency/biotinidase deficiency.
*as weight gain is a risk factor for polycystic ovary syndrome, patient weight must be carefully monitored (see section 4.4).

Nervous system disorders

• Very common: tremor.
• Common: extrapyramidal disorders, stupor*, sedation, seizures*, memory disorders, headache, nystagmus, nausea or dizziness.
• Uncommon: coma*, encephalopathy*, lethargy*, reversible Parkinsonian syndrome, ataxia, paresthesia, exacerbation of seizures (see section 4.4).
• Rare: cognitive disturbances of insidious and progressive onset (which may progress as far as complete dementia) and which are reversible a few weeks to a few months following treatment withdrawal.
*Cases of stupor or lethargy, sometimes leading to transient coma (encephalopathy) have been observed with valproate, regressing on treatment discontinuation or dose reduction. These states most often occur during multiple-agent therapy (particularly with phenobarbital or topiramate) or following a sudden increase in valproate doses.

Ear and labyrinth disorders

• Common: hearing loss.

Respiratory, thoracic and mediastinal disorders

• Uncommon: pleural effusion.

Gastrointestinal disorders

•Very common: nausea.

•Common: vomiting, gingival disorders (mainly gingival hyperplasia), stomatitis, epigastric pain, diarrhea that may occur in some patients at the beginning of treatment, but that generally resolves after a few days without treatment discontinuation.

•Uncommon: pancreatitis with possibly fatal outcome requiring early treatment discontinuation (see section 4.4).

Renal and urinary disorders

• Uncommon: renal failure.

• Rare: enuresis, urinary incontinence, tubulointerstitial nephritis.

Skin and subcutaneous tissue disorders

• Common: transient and/or dose-dependent hair loss, nail and nail bed disorders.

• Uncommon: angioedema, skin reactions, hair disorders (such as abnormal hair texture, change in hair color, abnormal hair growth).

• Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) or drug hypersensitivity syndrome.

Endocrine disorders

• Uncommon: inappropriate antidiuretic hormone secretion syndrome (IADHS), hyperandrogenism (hirsutism, virilism, acne, androgenic alopecia and/or increase in androgen hormone levels).

• Rare: hypothyroidism (see section 4.6).

Metabolism and nutrition disorders

• Common: hyponatremia.

• Rare: hyperammonemia* (see section 4.4), obesity.

*Isolated and moderate hyperammonemia with no changes in liver parameters can be observed, especially during multiple-agent therapy, and does not warrant treatment discontinuation.

However, cases of hyperammonemia with neurological symptoms (which may progress to coma) have also been reported, and require additional tests (see section 4.4).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

• Rare: myelodysplastic syndromes.

Vascular disorders

•Common: bleeding (see sections 4.4 and 4.8).

General disorders and administration site conditions

• Uncommon: hypothermia, non-severe peripheral edema.

Hepatobiliary disorders

• Common: liver disease (see section 4.4).

Reproductive system and breast disorders

• Common: menstrual irregularities.

• Uncommon: amenorrhea.

• Rare: impact on spermatogenesis (in particular, decreased sperm motility) (see section 4.6), polycystic ovaries.

Musculoskeletal and connective tissue disorders

• Uncommon: decreased bone mineral density, osteopenia, osteoporosis and fractures in patients receiving long-term treatment with valproate. The mechanism of action of valproate on bone metabolism is not known.

• Rare: acute systemic lupus erythematosus (see section 4.4), rhabdomyolysis (see section 4.4).

*These effects are mainly observed in children.

Psychiatric disorders

- Common: confused state, hallucinations, aggression*, agitation*, attention deficit disorders*.
- Rare: behavioral disturbances, psychomotor hyperactivity, learning disabilities*.

*These effects are mainly observed in children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: https://imis.tmda.go.tz/arrt or search for TMDA Adverse Reactions Reporting Tool in the Google Play or Apple App Store.

4.9. Overdose

The clinical signs of massive acute poisoning usually include a calm coma, which may be more or less deep, with muscle hypotonia, hyporeflexia, miosis, reduced respiratory autonomy and metabolic acidosis, hypotension and collapsus/ cardiovascular shock. A few cases of intracranial hypertension related to cerebral edema 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 favorable. However, a few deaths have been reported. In the event of overdose, the sodium content in formulations containing valproate can lead to hypernatremia.

1. PHARMACOLOGICAL PROPERTIES

1.1.Pharmacodynamic properties

Pharmacotherapeutic group: ANTIEPILEPTICS, ATC code: N03AG01. 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 two 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.

1.2.Pharmacokinetic properties

The various pharmacokinetic studies conducted on valproate have shown that:

- The bioavailability in the blood following oral administration is close to 100%.
- The volume of distribution is mainly limited to the blood and to the rapid-exchange extracellular fluids.

Valproate circulates in the CSF and in the brain.

- The half-life is 15 to 17 hours.
- Therapeutic efficacy usually requires a minimum serum concentration of 40 to 50 mg/l, with a wide range from 40 to 100 mg/l. If higher plasma levels prove necessary, the expected benefits must be weighed against the risk of occurrence of adverse effects,

particularly dose-dependent effects. However, levels remaining above 150 mg/l require a dose reduction.
• The steady-state plasma concentration is reached in 3 to 4 days.
• Valproate is highly protein-bound. Protein binding is dose-dependent and saturable.
• Valproate is excreted mainly in the urine, following metabolization by glucuronide conjugation and beta-oxidation.
• Valproate can be dialyzed, but hemodialysis only affects the free fraction of blood valproate (approximately 10%).
Valproate does not induce enzymes involved in the metabolic system of cytochrome P 450 in contrast with most other antiepileptics, it does not accelerate its own degradation or that of other substances, such as estrogen-progestogens and oral anticoagulants.

1.3.Preclinical safety data
Not applicable.

2. Pharmaceutical particulars
2.1. List of excipients
Methyl parahydroxybenzoate, propyl parahydroxybenzoate, sucrose, sorbitol, glycerin, cherry liquid, hydrochloride acid and purified water.

2.2.Incompatibilities
Not applicable

2.3. Shelf life
24 Months
In-use shelf life: one month after opening.

2.4. Special precautions for storage
Do not store above 30°C.
This medicine can be stored for one month after opening at a temperature.

2.5. Nature and contents of container
Vilapro® syrup is available in 150 ml amber glass bottle, CRC cap enclosed in a carton with spoon and leaflet.

2.6. Special precautions for disposal and other handling
Medicines should not be disposed of via wastewater or household waste.

1. Marketing authorization holder
Dar Al Dawa Development & Investment Co. Ltd.
P.O. Box 9364
Na'ur – Jordan

2. Marketing authorization number(s)
TAN 22 HM 0177

3. Date of first authorization/renewal of the authorisation

04th May, 2022

4. Date of revision of the text