SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Lepquity, 250 mg/5 mL, syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL contains valproic acid 250 mg.

Excipient(s) with known effect:

Contains methylparaben (0,12 % *w/v*) (preservative).

Propylene glycol 250 mg/5 mL (50 mg/mL).

Contains sodium hydroxide 69,5 mg per 5 mL.

Contains sugar (sucrose 2,35 g per 5 mL) and sweetener (sorbitol).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

Clear, colourless to light yellow solution with melon odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Lepquity is indicated for generalised seizures as well as for partial (focal) seizures, including complex partial seizures evolving to generalised seizures.

4.2 Posology and method of administration

Posology

The dosage (starting with a low initial dose) is determined by the medical practitioner and should not be arbitrarily altered or exceeded. The total daily dose should be administered in divided doses.

Epilepsy

Children:

Children weighing less than 20 kg may be given 15 – 20 mg per kg per day. In severe cases, the dosage can be increased at one-week intervals by 5 – 10 mg per kg daily to 40 mg per kg per day. But in these cases, the plasma valproate concentration of the patient must be monitored. Should the daily dose exceed 100 mg (e.g. 2 ml of Lepquity syrup), it should be administered in divided doses.

Children weighing more than 20 kg may be given 450 mg daily in divided doses, gradually increasing to establish control, usually at a level of 20 – 30 mg per kg per day.

Dosage in patients being treated with other anticonvulsant medicines, should be gradually reduced concurrently with the increase of the Lepquity dose.

Method of administration

Lepquity syrup is administered orally.

4.3 Contraindications

Lepquity is contraindicated in:

- Hypersensitivity to valproic acid or to any of the excipients listed in section 6.1.
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, especially medicine related.
- Porphyria.
- Pancreatic dysfunction.
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (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).

Treatment of epilepsy is contraindicated in:

- Pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6)
- Women of childbearing potential, unless supervised by a medical practitioner experienced in treating these conditions and the patient is informed of the risks of taking Lepquity and the pregnancy prevention program is fulfilled (see section 4.4 and 4.6).
- Women must not use Lepquity for preventing migraine when they are pregnant. Pregnancy should be excluded before starting treatment for migraine, and women should use effective contraception.

4.4 Special warnings and precautions for use

Special caution is required in the following cases

- Bone marrow abnormailities.
- Children younger than 3 years (as they are especially predisposed for hepatic damage).
- Haemorrhagic diathesis.
- Mentally retarded children.
- Renal dysfunction.
- Organic cerebral lesions.
- Severe epileptic seizure types.

Women of childbearing potential

Pregnancy Prevention Programme

Valproic acid contained in Lepquity has a high teratogenic potential and children exposed *in utero* to valproic acid have a high risk for congenital malformations and neuro-developmental disorders (see section 4.6).

Lepquity is contraindicated in the following situation

With treatment of epilepsy:

- 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 Pregnancy Prevention Programme are

fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The medical practitioner must ensure that:

- individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neuro-developmental disorders, including the magnitude of these risks for children exposed to valproic acid, contained in Lepquity, *in utero.*
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with Lepquity.
- the patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy.
- the patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- the patient understands the need to urgently consult her medical practitioner in case of pregnancy.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with Lepquity use.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pharmacists or healthcare professionals must ensure that:

- patients are advised not to stop their Lepquity medication and to immediately contact a medical

practitioner in case of planned or suspected pregnancy.

Female children

- The medical practitioner must ensure that parents/caregivers of female children understand the need to contact the medical practitioner once the female child using Lepquity experiences menarche (see section 4.3).
- The medical practitioner must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neuro-developmental disorders including the magnitude of these risks for children exposed to valproic acid, contained in Lepquity, *in utero* (see section 4.3).
- In patients who have experienced menarche, the medical practitioner must reassess the need for Lepquity therapy and consider alternative treatment options. If Lepquity is the only suitable treatment, the need for using effective contraception and all other conditions of the ***Pregnancy Prevention Programme*** must be discussed. Every effort should be made by the medical practitioner to switch female children on Lepquity to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test

Pregnancy must be excluded before start of treatment with Lepquity. Treatment with Lepquity must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed Lepquity must use effective contraception without interruption during the entire duration of treatment with Lepquity. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

Annual treatment reviews by a medical practitioner

The medical practitioner should review at least annually whether Lepquity is the most suitable treatment for the patient. The medical practitioner should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

If a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess Lepquity therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the risks of Lepquity for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using Lepquity becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with Lepquity and consider alternative treatment options. The patients with Lepquity-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.3 and 4.6).

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to Lepquity during pregnancy, educational materials are provided to reinforce the warnings, provide guidance regarding use of Lepquity in women of childbearing potential and includes the details of the pregnancy prevention program.

An annual risk acknowledgement form needs to be completed at time of treatment initiation and during each annual review of Lepquity treatment by the medical practitioner.

Special warnings

Liver dysfunction:

Lepquity may cause hepatic dyfunction including fatal hepatic failure. This may be independent of dosage level and usually occurs during the first 6 months of treatment and children are at greater risk. This may be preceded

by non-specific symptoms such as loss of seizure control, malaise, weakness and lethargy. If clinical symptoms of hepatic damage (recurrent epigastric complaints, anorexia, vomiting, fatigue, asthenia, icterus, ascites, hepatic encephalopathy) occur, treatment must be discontinued under the supervision of a medical practitioner. Hepatic function impairment may progress in spite of discontinuation of medication. Sudden discontinuation of Lepquity may lead to an increase in seizure frequency.

Patients experiencing abdominal pain, symptoms of organic damage or haemorrhagic disorders, should have serum amylase and lipase checked. At the first indication of pancreatitis, treatment must be stopped under the supervision of the medical practitioner.

Liver function tests, coagulation parameters and determination of serum amylase and lipase, should be carried out before starting therapy, and also at 2-monthly intervals during the first 6 months of therapy. Thereafter, the aforementioned tests should be carried out when the dose is increased. Lepquity should be discontinued if one of the following occurs: hypofibrinogenemia, coagulation disorders, increase in transaminases to their triple value, increases in alkaline phosphatase or serum bilirubin, symptoms or signs of toxic hepatitis. If only transaminases are slightly increased, the dose should be reduced and liver function, as well as coagulation parameters should be monitored.

Pancreatitis:

Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Lepquity should be discontinued.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines, such as

Lepquity. A meta-analysis of randomised placebo- controlled trials of anti-epileptic medicines has also shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for Lespio. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Precautions

Haematological:

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8).

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Systemic lupus erythematosus:

Although immune disorders have only rarely been noted during the use of valproic acid, the potential benefit of Lepquity should be weighed against its potential risk in patients with systemic lupus erythematosus (see also section 4.8).

Hyperammonaemia:

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with Lepquity.

Weight gain:

Lepquity frequently 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 (see section 4.8).

Carbapenem medicines:

The concomitant use of valproic acid, as in Lepquity, and carbapenem medicines is not recommended (see section 4.5).

Diabetic patients:

Valproic acid 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 known or suspected mitochondrial disease:

Lepquity may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproic acid-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 gene for the mitochondrial enzyme polymerase γ (POLG, 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).

Lepquity is not indicated for the treatment of manic episodes in bipolar disorder in children.

Lepquity contains propylene glycol, sorbitol, sugar and sodium:

Propylene glycol:

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates and children less than 5 years old.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Sorbitol:

Lepquity contains 320 mg sorbitol in each 5 ml dose. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take Lepquity. 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 medicines for oral use may affect the bioavailability of other medicines for oral use administered concomitantly.

Sugar (sucrose):

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Lepquity.

Sodium:

Lepquity contains 40 mg sodium per 5 mL, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult/child.

4.5 Interaction with other medicines and other forms of interaction

Effects of Lepquity on other medicines:

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

Lepquity may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised, and dosage should be adjusted when appropriate.

Phenobarbital (Phenobarbitone)

Lepquity increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

Primidone

Lepquity increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin

Lepquity decreases phenytoin total plasma concentration. Moreover, Lepquity increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore, clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

Carbamazepine

Clinical toxicity has been reported when Lepquity was administered with carbamazepine as Lepquity may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

Lepquity may reduce lamotrigine metabolism and increase its mean half-life. Dosages should be adjusted (lamotrigine dosage decreased) when appropriate. The co-administration of lamotrigine and Lepquity might increase the risk of rash.

Zidovudine

Lepquity may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Vitamin K-dependent anticoagulants

The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid, contained in Lepquity. The prothrombin time should be closely monitored.

Temozolomide

Co-administration of temozolomide and Lepquity may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other medicines on Lepquity

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid plasma concentrations. Dosages should be adjusted to blood levels in case of combined therapy.

On the other hand, combination of felbamate and Lepquity may increase valproic acid plasma concentration. Lepquity dosage should be monitored.

Anti-malarial medicines

Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Lepquity may need adjustment.

Highly protein bound medicines

In case of concomitant use of Lepquity and highly protein bound medicines (e.g., aspirin), free valproic acid plasma levels may be increased.

Cimetidine or erythromycin

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant

use with cimetidine or erythromycin.

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

Decreases in blood levels of valproic acid, contained in Lepquity, have been reported when it is co-administered with carbapenem medicines resulting in a 60 – 100 % decrease in valproic acid levels within two days.

Due to the rapid onset and the extent of the decrease, co-administration of carbapenem medicines in patients stabilised on Lepquity should be avoided (see section 4.4).

Cholestyramine

Cholestyramine may decrease the absorption of valproic acid, contained in Lepquity.

Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease valproic acid, contained in Lepquity, plasma level when co-administered.

Although formal interaction studies have not been performed, available data suggest a reduction ranging from 40 % to 77,5 % in valproic acid plasma levels. Patients using protease inhibitors such as ritonavir for the treatment of HIV infection should be carefully monitored for decreased control of their epilepsy/mood status of bipolar patients if also treated with Lepquity.

Other interactions

Newer anti-epileptics (including topiramate and acetazolamide)

Caution is advised when using Lepquity in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Oestrogen containing medicines

Valproic acid, contained in Lepquity, usually has no enzyme-inducing effects; consequently, Lepquity does not reduce efficacy of oestroprogestative medicines in women receiving hormonal contraception, including the oral contraceptive pill.

Effect of Lepquity on laboratory parameters

Valproic acid, contained in Lepquity, is partially eliminated in the urine as a keto-metabolite which may lead to a false positive result of the urine ketone test in diabetic patients. Depending on the plasma concentration, valproic acid, contained in Lepquity, may lead to a displacement of thyroid hormones from their protein binding sites, and also to their more rapid metabolism, so that thyroid function tests may incorrectly lead to a suspicion of hypothyroidism.

Cannabidiol

In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25

mg/kg and valproic acid, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19 % of patients.

Appropriate liver monitoring should be exercised when Lepquity 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.

4.6 Fertility, pregnancy and lactation

Lepquity is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Lepquity is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Program are fulfilled (see sections 4.3 and 4.4).

Women of childbearing potential / Contraception in males and females

Lepquity should not be used in female children, in female adolescents, in women of child-bearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of child-bearing 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.

Teratogenicity and developmental effects

Both Lepquity monotherapy and Lepquity polytherapy including other anti-epileptics are associated with abnormal pregnancy outcomes. Anti-epileptic polytherapy that includes Lepquity may be associated with a

greater risk of congenital malformations than Lepquity monotherapy.

Valproic acid, contained in Lepquity, was shown to cross the placental barrier both in animal species and in humans.

Congenital malformations:

Data derived from a meta-analysis (including registries and cohort studies) have shown that 10,73 % of children born to epileptic women exposed to valproic acid 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 or major malformations. The most frequent types of malformations include neural tube defects, facial dysmorphia, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius) and multiple anomalies involving various body systems.

In utero exposure to Lepquity may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental disorders:

Data have shown that exposure to Lepquity *in utero* can have adverse effects on mental and physical development of the exposed children. This risk appears to be dose-dependent, but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed *in utero* to Lepquity 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 (age 6) with a history of Lepquity exposure *in utero* was on average 7 - 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to Lepquity that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Available data show that children exposed to Lepquity *in utero* are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general population.

Limited data suggests that children exposed to Lepquity *in utero* may be more likely (approximately 1,5-fold) to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

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

If a woman plans a pregnancy:

For the epilepsy indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy, must reassess the Lepquity therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued. If switching is not possible, the woman should receive further counselling regarding the valproic acid, contained in Lepquity, risks for the unborn child to support her informed decision-making regarding family planning.

Pregnancy

Lepquity as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using Lepquity becomes pregnant, she must be immediately referred to a medical practitioner to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of Lepquity in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive Lepquity for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of Lepquity 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.

All patients with a valproic acid, contained in Lepquity, exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations.

Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects of malformations due to valproic acid, contained in Lepquity, exposure.
Lepquity therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with Lepquity for the patient by a medical practitioner experienced in the management of epilepsy.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported less frequently in neonates whose mothers have taken valproic acid, contained in Lepquity, during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenaemia and/or to decrease in other coagulation factors. Afibrinogenaemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital (phenobarbitone) and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproic acid, contained in Lepquity, during the third trimester of their pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproic acid, contained in Lepquity, during pregnancy.

Withdrawal syndrome (in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproic acid, contained in Lepquity, during the last trimester of pregnancy.

Breastfeeding

Valproic acid, contained in Lepquity, is excreted in breastmilk with a concentration ranging from 1 % to 10 % of total maternal serum levels.

Haematological disorders have been shown in breastfed newborns/infants of women treated with valproic acid, contained in Lepquity (see section 4.8).

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Lepquity therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. No adverse effects in the nursing infant have been reported. The decision to allow the patient to breastfeed should be taken with regard to all the known facts.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproic acid, contained in Lepquity (see section 4.8).

Lepquity administration may also impair fertility in men (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

Use of Lepquity may provide seizure control such that the patient may be eligible to hold a driving licence.

Lepquity has a moderate influence on the ability to drive and use machines.

Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines (see section 4.5).

4.8 Undesirable effects

a. Summary of safety profile

Side-effects occur in less frequent cases and are most frequently seen when plasma levels exceed 100 mg/l or when Lepquity is used in combination therapy.

b. Tabulated list of adverse reactions

Blood and lymphatic system disorders:	
Frequent	Thrombocytopenia
Less frequent	Anaemia, leucopenia, pancytopenia, reduction of fibrinogen, reversible increase in bleeding time, spontaneous bruising or bleeding
Immune system disorders:	
Less frequent	Allergic reactions (ranging from rash to hypersensitivity reactions)
Metabolism and nutrition disorders:	
Frequent	Hyperammonaemia (see section 4.4)
Less frequent	Obesity
Nervous system disorders:	
Less frequent	Sedation, lethargy and confusion occassionally progressing to stupor, sometimes with associated hallucinations or convulsions, diplopia, encephalopathy and coma, reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy, dose-related ataxia and fine postural tremor, increase in alertness, aggression, hyperactivity and behavioural deterioration
Ear and labyrinth disorders:	
Less frequent	Hearing loss
Vascular disorders:	
Less frequent	Vasculitis
Gastrointestinal disorders:	

Frequent	Nausea, gastralgia, diarrhoea
Less frequent	Pancreatitis, sometimes lethal (see section 4.4)
Hepatobiliary disorders:	
Frequent	Increased liver enzymes
Less frequent	Liver dysfunction, severe liver damage, including hepatic failure sometimes resulting in death (see section 4.4)
Skin and subcutaneous tissue disorders:	
Frequent	Nail and nail bed disorders
Less frequent	Cutaneous reactions such as exanthematous rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, transient hair loss, hirsutism, acne
Musculoskeletal and connective tissue disorders:	
Less frequent	Decreased bone mineral density, osteopenia, osteoporosis and fractures
Renal and urinary disorders:	
Less frequent	A reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria)
Reproductive system and breast disorders:	
Less frequent	Amenorrhoea and irregular periods, gynaecomastia
Congenital, familial and genetic disorders:	
Less frequent	Congenital malformations and developmental disorders (see section 4.4 and section 4.6)
General disorders:	
Less frequent	Non-severe peripheral oedema, increase in weight (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse medicine reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Acute overdose may lead to coma, accompanied by areflexia and central respiratory depression. Treatment should include induced vomiting, administration of activated charcoal, gastric lavage, assisted ventilation, forced diuresis and other supportive measures.

Naloxone has been reported to reverse the CNS-depressant effects of overdosage (also see under section 4.5).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anti-convulsants including anti-epileptics.

Pharmacotherapeutic group: Anti-epileptics, fatty acid derivatives, ATC code: N03AG01.

The anticonvulsant action of valproic acid may be related to increased levels of gamma-aminobutyric acid (GABA) in the brain by inhibiting aminobutyrate aminotransferase. GABA inhibits pre- and post-synaptic discharges.

5.2 Pharmacokinetic properties

Absorption

The half-life of valproate is usually reported to be within the range of 8-20 hours. It is usually shorter in children. In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40 - 100 mg/litre (278 - 694 µmol/l). This reported range may depend on time of sampling and presence of co-medication.

Distribution

The percentage of free (unbound) medicine is usually between 6 % and 15 % of total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of Lepquity may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Special populations

Paediatric population:

Based on published literature, in paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults.

In children aged 2-10 years, valproate clearance is 50 % higher than in adults. Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (pH adjustment)

Methylparaben (preservative)

Melon flavour 50997 C

Propylene glycol (E 1520)

Sodium hydroxide

Sorbitol liquid (E 420)

Sucrose

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Lepquity syrup is packed in amber glass bottle 100 mL and covered by aluminium cap and placed into a folding box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

57/2.5/0189

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 May 2025

10. DATE OF REVISION OF THE TEXT