VALEPTIC CR has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the foetus resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities.

Exposure to VALEPTIC CR in utero is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD).

VALEPTIC CR treatment should be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and VALEPTIC CR should not be prescribed if the relevant Risk Minimisation Measures/Pregnancy Prevention Programme, cannot be implemented and supervised and patients are not committed to adhere to these measures.

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VALEPTIC CR 300 (Controlled release tablets)

VALEPTIC CR 500 (Controlled release tablets).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALEPTIC CR 300: Each controlled release tablet contains 300 mg sodium valproate

VALEPTIC CR 500: Each controlled release tablet contains 500 mg sodium valproate

Excipients with known effect:
Sodium and soy lecithin (E322).
VALEPTIC CR 300 contains 42 mg sodium and 2,1 mg soy lecithin per tablet.
VALEPTIC CR 500 contains 69 mg sodium and 2,9 mg soy lecithin per tablet.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Controlled release tablets.

VALEPTIC CR 300: White or almost white, un-scored and film-coated, round, convex tablet with a diameter of 12,2 – 12,8 mm.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
VALEPTIC CR is indicated for use in the treatment of *generalised epilepsy*, particularly with the following patterns of seizures:

- absence
- myoclonic
- tonic-clonic
- atonic
- mixed.

VALEPTIC CR is indicated for use in *partial epilepsy*, for the treatment of:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut).

VALEPTIC CR is indicated for the acute and maintenance treatment of manic episodes associated with bipolar disorders in adults.

4.2 Posology and method of administration

Posology

VALEPTIC CR 300 and VALEPTIC CR 500:

- Daily dosage requirements may vary according to age and body weight.
- May be given once or twice daily.

VALEPTIC CR is a controlled release formulation which minimises fluctuations in plasma concentration and ensures a more even plasma concentration throughout the day.

In patients where adequate control has been achieved, VALEPTIC CR formulations are interchangeable with other conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosages of VALEPTIC CR in the treatment of epilepsy:

Adults:

Dosage should start at 600 mg/day, in divided doses where applicable, increasing by 5 to 10 mg/kg/day at weekly intervals until control is achieved.

This is generally within the range of 1 000 to 2 000 mg/day (i.e. 20-30 mg/day body mass).

If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day, or one other anti-epileptic medicine may be added at a low dosage.

In patients already receiving other therapy, the same pattern should be followed.

If increased sedation occurs, dosage of barbiturates or benzodiazepines (e.g., lorazepam) should be reduced as that of VALEPTIC CR is increased (see “Initiation of VALEPTIC CR and combination therapy” below).

Dosage of both VALEPTIC CR and other agents should be adjusted, during the stabilisation period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with VALEPTIC CR alone.

Dosages of VALEPTIC CR for the treatment and prevention of mania associated with bipolar disorders:

- The recommended initial dose is 1 000 mg/day.
- The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effect.
- Doses should be adjusted according to individual clinical response.
- Prophylactic treatment should be established individually with the lowest effective dose.

Missed doses of VALEPTIC CR:

If dosing schedule is:

Once daily: Take dose as soon as possible; skip the missed dose if not remembered until the next day. No doubling of doses is recommended.

Twice daily: Take dose within 6 hours if remembered, taking the remaining dose for that day at equally spaced intervals. No doubling of doses is recommended.

Special Populations:

Patients with renal insufficiency:

- It may be necessary to decrease dosage.
- Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2**)**.

Elderly patients:

- Dosage should be determined by seizure control.
- The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free medicine is increased.
- This may affect the clinical interpretation of plasma valproic acid levels.

Initiation of VALEPTIC CR and combination therapy:

- If patients are already on other anticonvulsants and therapy with VALEPTIC CR is initiated, then the dose of the other anticonvulsants should be tapered slowly if they are to be discontinued.
- Initiation of VALEPTIC CR should then be gradual with target dose being reached after about 2 weeks.

- In certain cases, it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants, which induce liver enzyme activity e.g., phenytoin, phenobarbitone and carbamazepine (see section 4.5).
- Once known enzyme inducers have been withdrawn, or if side effects such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of VALEPTIC CR.
- When barbiturates are being administered concomitantly and particularly if sedation occurs, the dosage of barbiturates should be reduced (see “Dosages of VALEPTIC CR in the treatment of epilepsy” above).

General considerations of VALEPTIC CR:

- The therapeutic concentration of valproate in plasma is approximately 30-100 µg/mL.
- Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary.
- However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2).

Paediatric population

The safety and efficacy of VALEPTIC CR have not been evaluated in the treatment of mania in bipolar disorder in patients under 18 years of age.

Method of administration

VALEPTIC CR 300 and VALEPTIC CR 500:

Should be administered orally.

Should preferably be taken with or after food.

Tablets should be swallowed whole, if necessary, with a little water (but not with aerated mineral water).

Tablets should not be crushed or chewed.

4.3 Contraindications

VALEPTIC CR is contraindicated for use in:

- Patients who are hypersensitive to sodium valproate, to peanuts or soya or to any ingredients used in VALEPTIC CR (see section 6.1).
- Patients who are pregnant or lactating (see section 4.4 and 4.6).

With the treatment of epilepsy:

- In pregnancy, unless there is no suitable alternative treatment
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled

With the treatment of bipolar disorder:

- In pregnancy
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled
- Active liver disease, including the following (see section 4.4)
- acute hepatitis
- chronic hepatitis
- personal or family history of hepatic dysfunction especially medicine-related
- hepatic porphyria
- Patients with known urea cycle disorders (see section 4.4)
- Valproate as contained in VALEPTIC CR is contraindicated in patients with known mitochondrial disease (e.g., Alpers–Huttenlocher syndrome) caused by nucleus gene mutations coding the mitochondrial polymerase gamma (POLG) enzyme, and in children under 2 years of age with suspected POLG mutation-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

Treatment with VALEPTIC CR should be initiated and supervised by a medical practitioner experienced in the management of epilepsy and bipolar disorders.

Women of childbearing potential

Pregnancy Prevention Programme:

VALEPTIC CR 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).

VALEPTIC CR is contraindicated in the following situations:

With treatment of epilepsy:

- during 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 programme are fulfilled (see sections 4.3 and 4.6).

With treatment of bipolar disorder:

- in pregnancy (see sections 4.3 and 4.6)
- in women of childbearing potential, unless the conditions of the 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 are evaluated in each case, discussing the matter with the patient in order to guarantee her engagement, discussing therapeutic options and ensuring her understanding of the risks and the measures needed to minimise the risks
- the potential for pregnancy is assessed in all female patients
- the patient has understood the risks of congenital malformations and neurodevelopmental disorders and is aware of them, including the magnitude of these risks for children exposed to valproate *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 (refer to “Contraception” in this section), without interruption during the entire duration of treatment with VALEPTIC CR
- the patient understands the need for regular (at least annual) treatment reviews by a medical practitioner experienced in the management of epilepsy or bipolar disorder
- the patient understands the need to consult her doctor as soon as she plans a pregnancy in order to ensure timely discussion and a switch to alternative treatment prior to conception and before contraception is discontinued
- the patient understands the need to immediately consult her doctor in case of pregnancy
- the patient has received the patient guide
- the patient has acknowledged that she has understood the risks and necessary precautions associated with valproate use (annual risk acceptance form).

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

Pharmacists or healthcare professionals must ensure that:

- the patient card is provided with every VALEPTIC CR dispensing and that the patients understand its content
- patients are advised not to stop their VALEPTIC CR medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Female children:

- Medical practitioners must ensure that parents/guardians of girls understand the need to contact a medical practitioner once the girl using VALEPTIC CR experiences menarche (see section 4.3).
- The medical practitioner must ensure that parents/guardians of girls who have experienced menarche are given comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for infants exposed to valproate *in utero* (see section 4.3).
- In patients who have experienced menarche, the prescribing medical practitioner must reassess the need for VALEPTIC CR therapy annually and consider an alternative treatment. If VALEPTIC CR is the only suitable treatment, the need to use effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the medical practitioner to switch girls to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test:

Pregnancy must be excluded before start of treatment with VALEPTIC CR. Treatment with VALEPTIC CR 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 have been prescribed VALEPTIC CR must use effective contraception without interruption throughout their treatment with VALEPTIC CR. These patients must be given comprehensive information on contraception and should be referred for contraceptive guidance if they are not using effective contraception. At least one effective method of contraception (preferably a user-independent form such as an intrauterine device or implant) or two complementary forms of contraception including a barrier method should be used. When choosing the method of contraception, individual circumstances should be evaluated in each case, involving the patient in the discussion in order to guarantee her engagement and compliance with the chosen methods. Even if she has amenorrhoea, she must follow all the advice on effective contraception (see section 4.3).

Annual treatment review by a medical practitioner:

A medical practitioner should at least annually review whether VALEPTIC CR is the most suitable treatment for the patient. The medical practitioner should discuss the annual risk acceptance form and ensure that the patient has understood its content at treatment initiation and during each annual treatment review.

Pregnancy planning:

If a woman using the medicine to treat epilepsy is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess VALEPTIC CR therapy and consider an alternative treatment. 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 VALEPTIC CR treatment for the unborn child to support her informed decision regarding family planning (see section 4.3).

For the indication of bipolar disorder, if a woman is planning to become pregnant, a medical practitioner experienced in the management of bipolar disorder must be consulted and treatment with VALEPTIC CR should be discontinued and, if necessary, switched to an alternative treatment prior to conception and before contraception is discontinued (see section 4.3).

In case of pregnancy:

If a woman using VALEPTIC CR becomes pregnant, she must be immediately referred to a medical practitioner for a re-assessment of treatment with VALEPTIC CR and consideration of

an alternative treatment. Patients with a valproate-exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology for evaluation and counselling regarding the exposure during pregnancy (see section 4.6).

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to VALEPTIC CR during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of VALEPTIC CR in women of childbearing potential and includes the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using VALEPTIC CR (see section 4.3).
An annual risk acknowledgement form needs to be completed at time of treatment initiation and during each annual review of VALEPTIC CR treatment by the medical practitioner.

Children (male and female) less than 18 years of age:
Epilepsy:
Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving VALEPTIC CR (see section 4.8). Current evidence is inconclusive as to the possibility of harm to reproductive organs, skeletal system growth or developing brain of patients less than 18 years of age.

In male children less than 18 years of age, VALEPTIC CR should be used with caution and in alignment with guidelines on the use of antiepileptics.

VALEPTIC CR can be used in female children less than 18 years of age only if there is no suitable safer alternative therapy or alternate therapy have failed to control the epilepsy. In addition, for female children, ensure that the conditions of the pregnancy prevention programme are met (see sections 4.4 and 4.6).

Bipolar disorder:
VALEPTIC CR is not indicated for the treatment of manic episodes in bipolar disorder in children (see section 4.1).

Adult males intending procreation:

Valproate as contained in VALEPTIC CR has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see section 4.4 and 4.6). The medical practitioner should discuss with adult males their intent to procreate, when prescribing VALEPTIC CR. If procreation is intended, VALEPTIC CR should be used only if alternative treatment options are not suitable.

Severe liver damage

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, have been reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3 years, the incidence of occurrence is reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration, especially in patients at risk (see above: 'Conditions of occurrence'):

- non-specific symptoms, usually of sudden onset, such as asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

Patients (or their family for children) should be instructed to report immediately any such signs to a medical practitioner should they occur. Investigations including clinical examination and laboratory assessment of liver function should be undertaken immediately.

Detection:

- Liver function tests should be performed before administration of VALEPTIC CR and then liver function should be periodically monitored during the first 6 months of therapy.
- Increased liver enzymes may occur, particularly at the beginning of therapy.
- More extensive biological investigations (including Prothrombin Index/Prothrombin Time [INR/PT]) are recommended in these patients and dosage adjustments and tests should be repeated as necessary.
- Amongst usual investigations, tests which reflect protein synthesis, particularly INR/PT, are most relevant.
- Confirmation of an abnormally low INR/PT, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of therapy with VALEPTIC CR.
- 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).
- As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued since they employ the same metabolic pathway.
- The concomitant use of salicylates should be avoided in children due to the risk of liver toxicity.

Pancreatitis

Severe pancreatitis, which may result in fatalities, may occur less frequently (see section 4.8).

Exceptional cases of pancreatitis may occur, therefore patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, VALEPTIC CR should be interrupted.

- Young children are at particular risk.
- This risk decreases with increasing age.
- Severe seizures, neurological impairment or anti-convulsant therapy may be risk factors.
- Hepatic failure with pancreatitis increases the risk of fatal outcome.

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 (see section 5.2).

Although immune disorders have been only exceptionally noted during the use of VALEPTIC CR, the potential benefit should be weighed against its potential risk in patients with systemic lupus erythematosus.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptics including VALEPTIC CR, in several indications. A meta-analysis of randomised, placebo-controlled antiepileptic studies also shown increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known. Therefore, patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

Carbapenem medicine

The concomitant use of VALEPTIC CR and carbapenem medicines is not recommended (see section 4.5).

Patients with a known or suspected mitochondrial disease

VALEPTIC CR may trigger or worsen clinical signs of mitochondrial disorders. These disorders are caused by mutations of the mitochondrial DNA and the nucleus POLG gene. In particular, acute liver failure and liver-related deaths have been associated with VALEPTIC CR treatment 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).

Aggravated convulsions

Some patients may experience a reversible worsening of convulsion frequency and severity (including status epilepticus) instead of an improvement, or the onset of new types of convulsions with valproate as contained in VALEPTIC CR. In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

Haematological

Blood tests (blood count, including thrombocyte levels and bleeding and coagulation time tests) are recommended before starting treatment or before surgical procedures, and if the patient has 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 (see sections 4.2 and 5.2).

Systemic lupus erythematosus

New development and exacerbation of Systemic Lupus Erythematosus (SLE) may occur. The potential benefit of VALEPTIC CR should be weighed against its potential risk in patients with systemic lupus erythematosus.

Urea cycle disorders

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment with VALEPTIC CR because of the risk of hyperammonaemia (see section 4.3).

Weight gain

Patients should be warned of the risk of weight gain at the initiation of therapy as weight gain is a risk factor for polycystic ovarian syndrome and appropriate strategies should be adopted to minimise it (see section 4.8)

Diabetic patients

VALEPTIC CR is eliminated mainly through the kidneys, in diabetic patients, partly in the form of ketone bodies. This may give false positive readings in the urine testing of possible diabetics.

Carnitine palmitoyltransferase (CPT) type II deficiency

Patients with carnitine palmitoyltransferase II (CPT II) deficiency should be warned about a higher than normal risk for rhabdomyolysis during VALEPTIC CR use.

Alcohol

Alcohol intake is not recommended during treatment with VALEPTIC CR.

Paediatric population

Among the oral pharmaceutical forms, the following formulations are more appropriate for administration to children less than 11 years (oral solution and crushable tablets).

Excipients

VALEPTIC CR 300 mg controlled-release tablets contain 42 mg sodium per tablet, equivalent to 2,1 % of the WHO recommended adult maximum daily intake of 2 g sodium.

VALEPTIC CR 500 mg controlled-release tablets contain 69 mg sodium per tablet, equivalent to 3,5 % of the WHO recommended adult maximum daily intake of 2 g sodium.

The daily dose of VALEPTIC CR higher than 3,000 mg is equivalent to 20 % of the WHO recommended adult maximum daily intake of 2 g sodium. This dose is considered high in sodium. This should be taken into account particularly for those on a low sodium diet.

VALEPTIC CR contains soya lecithin (E322). Patients who are allergic to peanut or soya should not use this VALEPTIC CR (see section 4.3).

4.5 Interactions with other medicines and other forms of interaction

VALEPTIC CR may interact with other medicines or other medicines may interact with VALEPTIC CR (see section 5.2).

Effects of VALEPTIC CR on other medicines:

Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

VALEPTIC CR may potentiate the effect of these psychotropic medicines such as neuroleptics, MAO inhibitors including linezolid, antidepressants and benzodiazepines (see section 4.7, “Effects on ability to drive and use machines”). Clinical monitoring is advised and dosage adjustments carried out where appropriate.

Olanzapine

VALEPTIC CR can reduce the olanzapine plasma concentrations.

Phenobarbital

VALEPTIC CR increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Clinical monitoring is recommended throughout the first 15 days of combined treatment, with immediate reduction of phenobarbital doses if sedation occurs. Phenobarbital plasma levels should be determined where appropriate.

Primidone

VALEPTIC CR increases primidone plasma levels with exacerbation of its adverse effects (e.g., sedation). These effects cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin

VALEPTIC CR decreases phenytoin total plasma concentration. Moreover, it increases the free form of phenytoin with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism).

Clinical monitoring is recommended. If phenytoin plasma levels are to be determined, the free form should also be evaluated.

Carbamazepine

VALEPTIC CR may cause clinical toxicity as it may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended, especially at the beginning of combined therapy with VALEPTIC CR, with dosage adjustment when appropriate.

Lamotrigine

VALEPTIC CR may reduce the metabolism of lamotrigine and increase its mean half-life. Dosages should be adjusted (lamotrigine dosage decreased) where appropriate. The risk of rash may be increased by co-administration, but this has yet to be proved.

Zidovudine

VALEPTIC CR may increase zidovudine plasma concentration leading to increased zidovudine toxicity.

Propofol

VALEPTIC CR can increase propofol blood concentrations. Reduction of the propofol dose should be considered if it is used concomitantly with valproate.

Nimodipine

In patients concomitantly treated with VALEPTIC CR and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

Temozolomide

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

Effects of other medicines on VALEPTIC CR:

Antidepressant and neuroleptics

May antagonise the anti-epileptic activity of VALEPTIC CR by lowering the seizure threshold. Dosage adjustments of VALEPTIC CR may need to be made.

Anti-epileptics

Anti-epileptics with enzyme inducing effects (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations (see section 4.2).

Dosages should be adjusted according to blood levels in case of combined therapy.

Valproic acid metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore, patients treated with those two medicines should be carefully monitored for signs and symptoms of hyperammonaemia.

However, when VALEPTIC CR is administered in combination with felbamate, valproate serum concentration may increase. VALEPTIC CR dosage should be monitored.

Anti-malarials

Mefloquine, when used concomitantly with VALEPTIC CR, may increase valproic acid metabolism, thereby causing convulsions.

Chloroquine may also lower the seizure threshold when administered concomitantly with VALEPTIC CR.

Highly protein bound medicines (e.g. aspirin)

Concomitant use with VALEPTIC CR may increase free serum levels of valproate.

Coumarin type anti-coagulants:

Concomitant use of VALEPTIC CR with vitamin K dependent factor anticoagulants (e.g. warfarin and other coumarin anticoagulants) may cause an increase in anti-coagulant effect of these medicines, due to displacement from plasma protein binding sites. Close monitoring of INR should be performed with concomitant use.

Cimetidine or erythromycin

Concomitant use of VALEPTIC CR with cimetidine or erythromycin may result in increased valproate serum levels (as a result of reduced hepatic metabolism).

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

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

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

treatment with these antibiotics cannot be avoided, close monitoring of VALEPTIC CR blood level should be performed.

Rifampicin

Rifampicin may decrease the valproic acid blood concentrations, inhibiting the therapeutic effect. It may be necessary to adjust the VALEPTIC CR dosage if it is used concomitantly with rifampicin.

Protease inhibitors

Proteasome inhibitors, such as lopinavir and ritonavir, reduce the valproate plasma concentration if administered concomitantly.

Although formal interaction studies have not been performed, available data suggest a reduction ranging from 40 % to 77,5 % in valproate 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 VALEPTIC CR.

Cholestyramine

Cholestyramine can reduce the valproate plasma concentration as contained in VALEPTIC CR if administered concomitantly.

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased VALEPTIC CR efficacy (see section 4.4). Consider monitoring valproate serum levels.

VALEPTIC CR usually has no enzyme inducing effect. As a result, in women who are receiving hormonal contraception, it does not reduce efficacy of oestrogen and/or progestogen-containing medicines (see section 5.2).

Other interactions:

Concomitant use of VALEPTIC CR and topiramate or acetazolamide has been associated with encephalopathy, metabolic acidosis and/or hyperammonaemia. Patients treated with these two medicines should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.

Quetiapine

Concomitant use of VALEPTIC CR and quetiapine can increase the risk of neutropenia/leukopenia.

Alcohol

Alcohol intake is not recommended during treatment with VALEPTIC CR.

4.6 Fertility, pregnancy and lactation

Pregnancy

VALEPTIC CR:

Is contraindicated for use during pregnancy and lactation (see section 4.3).

With the treatment of epilepsy:

- In pregnancy, unless there is no suitable alternative treatment

With the treatment of bipolar disorder:

- VALEPTIC CR should not be used in pregnancy for the treatment of bipolar disorder (see section 4.3).

VALEPTIC CR is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.

Pregnancy Exposure Risk related to VALEPTIC CR:

Both VALEPTIC CR monotherapy and VALEPTIC CR polytherapy including other anti-epileptics are associated with abnormal pregnancy outcomes. Anti-epileptic polytherapy that includes VALEPTIC CR may be associated with a greater risk of congenital malformations than VALEPTIC CR monotherapy.

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations:
Data from a meta-analysis (including registries and cohort studies) have shown that 10,73 % of children born to epileptic women exposed to EPILIM 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 common types of malformations include neural tube defects, facial dysmorphism, cleft lip palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius) and multiple anomalies involving various body systems.

Developmental/neurodevelopmental disorders:
Data have shown that exposure to VALEPTIC CR *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 have shown a risk of developmental problems of up to 30 to 40 % in pre-school children exposed to valproate (as in VALEPTIC CR) in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of VALEPTIC CR 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 VALEPTIC CR that the risk of intellectual impairment may be independent from maternal IQ.

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

There are also limited data suggesting that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD).

In view of the above data the following recommendations should be taken into consideration:
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 VALEPTIC CR 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 VALEPTIC CR risks for the unborn child to support her informed decision-making regarding family planning.

For the bipolar disorder indication, if a woman is planning to become pregnant, a medical practitioner experienced in the management of bipolar disorder must be consulted. Treatment with VALEPTIC CR should be discontinued prior to conception, and before contraception is discontinued. If needed, alternative treatment options should be considered (see section 4.3).

Pregnant women
VALEPTIC CR as treatment for bipolar disorder is contraindicated for use during pregnancy. VALEPTIC CR as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see section 4.3).

If a woman using VALEPTIC CR 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 VALEPTIC CR in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of VALEPTIC CR 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 VALEPTIC CR exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal medicine 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.

If appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may reduce the risk of neural tube defects. However, available evidence does not suggest this prevents the birth defects or malformations due to VALEPTIC CR exposure.

Risk in the neonate
Cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken VALEPTIC CR during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenaemia and/or to decrease in other coagulation factors; a fibrinogenaemia has also been reported and may be fatal.
However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by 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 VALEPTIC CR during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken VALEPTIC CR during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesias, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken EPILIM during the last trimester of pregnancy.

Breastfeeding
VALEPTIC CR is excreted in breast milk when given to breastfeeding mothers.
Concentration of valproate in breast milk is between 1 % and 10 % of maternal serum levels.

Cases of haematological changes and somnolence have been reported in infants of mothers taking VALEPTIC CR, when breastfeeding their infants.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels, and impairment of ovarian function and of fertility have been reported in female patients using VALEPTIC CR (see section 4.8).

VALEPTIC CR administration may also impair fertility in male patients (see sections 4.4 & 4.8). Fertility dysfunctions may not always be reversible after treatment discontinuation.

Very low concentrations of valproate have been detected in semen of males on treatment with VALEPTIC CR.

It is not known with certainty if fertility would be affected by VALEPTIC CR treatment in children less than 18 years of age, as valproate may interact with sex hormones.

4.7 Effects on 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

VALEPTIC CR may have side effects.

b) Tabulated summary of adverse reactions

MedDRA System organ class	**Frequent**	**Less frequent**
Immune system disorders		Allergic reactions.
Neoplasms benign, malignant and unspecified (incl.		Myelodysplastic syndrome

cysts and polyps)		
Endocrine disorders		Syndrome of Inappropriate Secretion of ADH (antidiuretic hormone) (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or increased androgen), hypothyroidism (see section 4.6)
Congenital and familial/genetic disorders		Teratogenicity (see section 4.6, *unknown frequency*)
Hepato-biliary disorders	Liver injury (see section 4.4)	
Blood and lymphatic system disorders:	Thrombocytopenia, anaemia	Pancytopenia, leucopenia, reduction of fibrinogen, increase in bleeding time usually without associated clinical signs and particularly with high doses (sodium valproate has an inhibitory effect on the second phase of platelet aggregation), bone marrow failure, including erythrocyte

		aplasia, agranulocytosis, macrocytic anaemia, macrocytosis.
Gastrointestinal disorders	Nausea, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, upper abdominal pain, diarrhoea (at start of treatment but they usually disappear after a few days without discontinuing the treatment)	Pancreatitis, which may be fatal (see section 4.4)
Nervous system disorders	Moderate hyper-ammonaemia without changes in liver function tests (which should not cause treatment discontinuation), hyper-ammonaemia associated with neurological symptoms. In such cases further investigations should be considered (see section 4.4), tremor, extrapyradimal	Coma*, lethargy* (see below), ataxia, encephalopathy*, parkinsonism, paraesthesia, reversible dementia associated with cerebral atrophy, cognitive disorder. * Stupor or lethargy sometimes leading to coma/encephalopathy have been described during therapy; this may be associated with an increase in the

	disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus, dizziness	occurrence of convulsions. These cases have most often been reported during combined therapy (in particular, with phenobarbitone or topiramate) or after a sudden increase in VALEPTIC CR doses. ***Children exposed in utero**:* Neurodevelopmental problems such as late walking and talking, poor language skills, memory problems, lower intellectual abilities, autistic syndrome and ADHD have been observed in children exposed *in utero* (see section 4.6).
Skin and subcutaneous tissue disorders	Hypersensitivity, alopecia (re-growth normally begins within six months, although the hair may become curlier than previously)	Cutaneous reactions such as exanthematous rash and in exceptional cases toxic epidermal necrolysis, Stevens-Johnsons syndrome

		and erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome
Metabolism and nutrition disorders	Hyponatraemia, increased weight (see section 4.4)	Hyperammonaemia, obesity. Hyperammonaemia without change in liver function tests may occur and should not cause treatment discontinuation. Hyperammonaemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered (see section 4.4)
Reproductive system and breast disorders	Dysmenorrhoea	Amenorrhoea, irregular periods, male infertility, polycystic ovary syndrome, impairment of ovarian function and of fertility in females
Vascular disorders	Haemorrhage (see section 4.4)	Vasculitis

Ear and labyrinth disorders	Deafness	
Eye disorders		Diplopia
Renal and urinary disorders	Urinary incontinence	Renal failure, enuresis, tubulointerstitial nephritis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with VALEPTIC CR therapy, but the mode of action is as yet unclear
Psychiatric disorders	Confusional state, aggression*, agitation*, disturbance in attention*	Abnormal behaviour*, psychomotor hyperactivity*, learning disorder*
	* These adverse drug reactions are principally observed in the paediatric population.	
Respiratory, thoracic and mediastinal disorders		Pleural effusion
Musculoskeletal and connective tissue disorders		Bone material density decreased, osteopenia, osteoporosis and fractures in patients on

		long-term therapy with VALEPTIC CR. The mechanism by which VALEPTIC CR affects bone metabolism has not been identified, development and worsening of systemic lupus erythematosus, rhabdomyolysis (see section 4.4)
General disorders and administration site conditions		Hypothermia, non-severe peripheral oedema
Investigations		Decreased coagulation factors (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Paediatric population

The safety profile of valproate as contained in VALEPTIC CR in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis.

These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance inattention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Clinical signs of acute massive overdose usually include:

Coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock (also see section 4.8).

Symptoms may however be variable and seizures may occur in the presence of very high plasma levels.

Cases of intracranial hypertension related to cerebral oedema may occur.

The presence of sodium content in the VALEPTIC CR formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdosage should be symptomatic

Administration of activated charcoal may be useful following ingestion.

Cardio-respiratory monitoring.

Assisted ventilation and other supportive measures.

Haemodialysis and haemoperfusion or Naloxone may be used.

Deaths may occur following massive overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Anti-epileptics, ATC Code: N03AG01

Sodium Valproate and **Valproic Acid** (Valproate) have anticonvulsant properties. The exact mode of action is not fully understood. However, the most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA); by affecting either further synthesis or further metabolism of GABA.

5.2 Pharmacokinetic properties

Absorption:

Valproic acid and its salts are rapidly and completely absorbed from the gastro-intestinal tract following oral administration. Peak plasma concentrations may occur in 1 to 4 hours but this can be delayed for several hours if valproic acid is administered in enteric-coated tablets, in prolonged release formulation or is ingested with meals. Sodium valproate bioavailability is close to 100 % following oral administration.

Distribution:

The apparent volume of distribution for valproate is approximately 0,2 litre/kg. Valproic acid concentration in cerebrospinal fluid is close to free plasma concentration. Steady-state plasma concentration is reached after 3 to 4 days, following oral administration. Valproate is highly bound to plasma protein (90 -95 %). Binding is dose dependent and saturable.

Metabolism:

Valproic acid is extensively metabolised in the liver. When given in therapeutic doses, most of the medicine is converted to the conjugate ester of glucuronic acid, while mitochondrial metabolism, principally by means of beta-oxidation, accounts for the remainder. Some of the metabolites have anticonvulsant activity. Sodium valproate does not increase its own degradation neither that of other medicines such as oestrogen and progestogen-containing medicines, but metabolism may be enhanced by certain other medicines that induce hepatic microsomal enzymes (see section 4.5).

Elimination:

Sodium valproate is mainly excreted in urine following metabolism via glucuro-conjugation and beta oxidation. Small amounts are excreted in faeces and expired air. The elimination half-life of

sodium valproate varies from approximately 8 to 20 hours, with the shorter half-lives occurring in epileptic patients receiving multiple therapy and the longer half-lives occurring in patients with hepatic impairment. Half-life is usually shorter in children due to a higher clearance.

Pharmacokinetics in Special Populations:

Renal Impairment:

In patients with severe renal insufficiency, it may be necessary to alter the dosage in accordance with free plasma valproic acid levels (see sections 4.2 and 4.4).

Other pharmacokinetic considerations:

- The effective therapeutic range for plasma valproic acid levels in epileptic patients is considered to be between 30 and 100 µg/mL (see section 4.2).
- This may be influenced by the presence of co-medication.
- The percentage of free (unbound) valproic acid may usually be between 6 % and 15 % of total plasma levels.
- The pharmacological (or therapeutic) effects of VALEPTIC CR are not clearly correlated with the total or free (unbound) plasma valproic acid levels.

In cases where measurement of plasma levels is considered necessary, thorough plasma levels should be used for therapeutic monitoring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone
Hypromellose
Magnesium stearate
Silica, colloidal anhydrous
PVA based aqueous moisture barrier coating system consisting of:
Lecithin
Polyvinyl alcohol
Talc
Titanium dioxide
Xanthum gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool, dry place, at or below 25 °C

Protect from light. Keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

VALEPTIC CR 300:

Glass amber bottle with a white aluminium tamper evident screw cap containing 100 tablets. The cap is lined with polyethylene. A white propylene desiccant capsule is added in the container. The amber glass containers are further packed in cardboard boxes pre-printed with the information in accordance with Act 101/1965.

VALEPTIC CR 500:

Glass amber bottle with a white aluminium tamper evident screw cap containing 100 tablets. The cap is lined with polyethylene. A white propylene desiccant capsule is added in the container. The amber glass containers are further packed in cardboard boxes pre-printed with the information in accordance with Act 101/1965.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685.
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

VALEPTIC CR 300: 44/2.5/0067

VALEPTIC CR 500: 44/2.5/0068

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 05 December 2013

10. DATE OF REVISION OF THE TEXT

28 August 2023