1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PROFESSIONAL INFORMATION HUMAN MEDICINE

SCHEDULING STATUS: S3

1. NAME OF MEDICINE

RUBILIM CR 200 mg (Prolonged release tablets)

RUBILIM CR 300 mg (Prolonged release tablets)

RUBILIM CR 500 mg (Prolonged release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

RUBILIM CR 200: each prolonged release tablet contains 133,2 mg sodium valproate and 58,0 mg valproic acid equivalent to 200 mg sodium valproate.

RUBILIM CR 300: each prolonged release tablet contains 199,8 mg sodium valproate and 87,0 mg valproic acid equivalent to 300 mg Sodium Valproate.

RUBILIM CR 500: each prolonged release tablet contains 333,0 mg sodium valproate and 145,0 mg valproic acid equivalent to 500 mg sodium valproate.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

RUBILIM CR 200 mg is a film coated, oblonged shaped and violet coloured prolonged release tablet.

RUBILIM CR 300 mg is a film coated, oblonged shaped and blue coloured prolonged release tablet.

RUBILIM CR 500 mg is a film coated, oblonged shaped and violet coloured prolonged release tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of generalised epilepsy, particularly with the following patterns of seizures:

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

as well as, for partial epilepsy:

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

RUBILIM CR for the treatment and prevention of mania associated with bipolar disorders.

4.2 Posology and method of administration

Posology

RUBILIM CR is a controlled release formulation, which reduces peak concentration and ensures a more even plasma concentration throughout the day. RUBILIM CR may be given once or twice daily.

Daily dosage requirements vary according to age and body weight.

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

Adults:

Dosage should start at 600 mg/day, where applicable in divided doses, increasing by 200 mg/day at three day intervals until control is achieved; this is generally within the range of 1 000 to 2 000 mg/day (i.e. 20 – 30 mg/kg 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 is observed, dosage of barbiturates or benzodiazepines (e.g. lorazepam) should be reduced as that of RUBILIM CR is increased; dosage of both RUBILIM CR and other medicines should be adjusted, during the stabilization period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with RUBILIM CR alone.

Children over 20 kg:

Initial dosage should be 400 mg/day irrespective of mass, where applicable in divided doses, with spaced increases until control is achieved. This is usually within the range of 20 to 30 mg/kg of body mass per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per day.

Children under 20 kg:

20 mg/kg of body mass per day; in severe cases, this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

RUBILIM 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.

<u>Special populations</u>

Use in the elderly:

Although the pharmacokinetics of RUBILIM CR is modified in the elderly, this is of limited clinical significance and 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 drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In 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)

Paediatric population:

The safety and efficacy of RUBILIM CR for the treatment of manic episodes in bipolar disorder have not been established in studies in patients aged less than 18 year (see section 4.4).

Combined therapy:

When starting RUBILIM CR in patients already on other anticonvulsants, these should be tapered slowly; initiation of RUBILIM CR therapy 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. 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 RUBILIM CR. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations:

The concentration of valproate in plasma that appears to be associated with therapeutic effects 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)

Method of administration

For oral use

RUBILIM CR should be taken with or without food. The tablets should be swallowed whole, if necessary, with a little water (but not aerated mineral water) and not crushed or chewed.

4.3 Contraindications

Hypersensitivity to sodium valproate and any of the excipients of RUBILIM CR listed in section 6.1.

Pregnancy and lactation (see section 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:

- Acute hepatitis.
- Chronic hepatitis.
- Personal or family history of hepatic dysfunction especially drug related.
- Hepatic porphyria.

- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding 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).
- Patients with known urea cycle disorders (see section 4.4).

4.4 Special warnings and precautions for use

Treatment with RUBILIM 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:

RUBILIM CR has a high teratogenic potential and children exposed *in utero* to RUBILIM CR have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

RUBILIM CR is contraindicated in the following situations:

With treatment of epilepsy:

- in pregnancy, unless there is no suitable alternative treatment (see section 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).

With treatment of bipolar disorder:

- in pregnancy (see section 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.3 and 4.6).

Conditions of the Pregnancy Prevention Programme:

The medical practitioner must ensure that:

- individual circumstances are 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 neurodevelopmental disorders, including the magnitude of these risks for children exposed to RUBILIM CR *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 RUBILIM CR.
- the patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy, or bipolar disorders.
- the patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timeous 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 RUBILIM CR use (Annual Risk Acknowledgement 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 RUBILIM CR dispensing and that the patients understand its content.
- patients are advised not to stop their RUBILIM CR medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

<u>Female children:</u>

- The medical practitioner must ensure that parents/caregivers of female children understand the need to contact the medical practitioner once the female child using RUBILIM CR experiences menarche.
- 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 neurodevelopmental disorders including the magnitude of these risks for infants exposed to RUBILIM CR *in utero.*
- In patients who experienced menarche, the medical practitioner must reassess the need for RUBILIM CR therapy annually and consider alternative treatment options. If RUBILIM CR 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 RUBILIM CR to alternative treatment before they reach adulthood.

Pregnancy test:

Pregnancy must be excluded before start of treatment with RUBILIM CR. Treatment with RUBILIM 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 are prescribed RUBILIM CR must use effective contraception without interruption during the entire duration of treatment with RUBILIM CR. 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, which includes a barrier method, should be used.

Individual circumstances should be evaluated in each case, when choosing the contraception method, and involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea, she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Medical practitioners should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a medical practitioner:

The medical practitioner should at least annually review whether RUBILIM CR 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:

For the indication of epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess RUBILIM 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 RUBILIM CR risks for the unborn child, to support her informed decision-making regarding family planning.

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 RUBILIM CR should be discontinued and, if needed, switched to an alternative treatment prior to conception and before contraception is discontinued.

In case of pregnancy

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

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 RUBILIM 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, RUBILIM CR should be used with caution and in alignment with guidelines on the use of antiepileptics.

RUBILIM 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 section 4.4 and 4.6).

Bipolar disorder:

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

Adult males intending procreation:

RUBILIM CR has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see section 4.6 and 4.8). The medical practitioner should discuss with adult males their intent to procreate, when prescribing RUBILIM CR. If procreation is intended, valproate should be used only if alternative treatment options are not suitable.

Liver dysfunction:

Conditions of occurrence:

Cases of severe liver damage resulting sometimes in fatalities have been reported.

Experience in epilepsy has indicated that patients most at risk especially in cases of multiple anticonvulsant therapy are infants and young children under the age of 3 with severe seizure disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease.

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

In most cases, such liver damage occurred during the first 6 months of therapy.

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, anorexia, lethargy, 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 biological assessment of liver function should be undertaken immediately.

Detection:

Liver function should be performed before and then periodically monitored during the first 6 months of therapy. Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of RUBILIM CR therapy. 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, has been reported. Young children are at particular risk. This risk decreased with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, RUBILIM CR should be discontinued.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines, including RUBILIM CR, in several indications. 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 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 antibiotics:

The concomitant use of RUBILIM CR and carbapenem antibiotics is not recommended (see Section 4.5).

Patients with known or suspected mitochondrial disease:

RUBILIM CR 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, acute liver failure and liver-related deaths have been associated with RUBILIM CR treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations

in the gene for 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.

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 (see section 5.2).

Systemic Lupus Erythematosus:

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

Hyperammonaemia:

RUBILIM CR may cause hyperammonaemia.

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with RUBILIM CR (see section 4.2).

Weight gain:

Patients should be warned of the considerable risk of weight gain at the initiation of therapy, and appropriate strategies should be adopted to minimise this (see section 4.8).

Carnitine palmitoyltransferase (CPT) type II deficiency patients:

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking RUBILIM CR.

Diabetic patients:

RUBILIM CR is excreted mainly through the kidneys, partly in the form of ketone bodies, and this may give false positive readings in the urine testing of diabetics.

Alcohol use during treatment with RUBILIM CR:

Alcohol intake is not recommended during treatment with RUBILIM CR.

4.5 Interaction with other medicines and other forms of interaction

Effects of RUBILIM CR on other medicines:

- Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

RUBILIM CR 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.

- Phenobarbitone

RUBILIM CR increases phenobarbitone 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 phenobarbitone doses if sedation occurs and determination of phenobarbitone plasma levels when appropriate.

- Primidone

RUBILIM CR 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

RUBILIM CR decreases phenytoin total plasma concentration. Moreover RUBILIM CR 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 RUBILIM CR was administered with carbamazepine as valproate may potentiate toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- Lamotrigine

RUBILIM CR may reduce lamotrigine metabolism and increase its mean half-life; dosages should be adjusted (lamotrigine dosage decreased) when appropriate. There are suggestions, yet to be proven, that the risk of rash may be increased by co-administration of lamotrigine with RUBILIM CR.

- Zidovudine

RUBILIM CR may raise zidovudine plasma concentration leading to increase zidovudine toxicity.

- Nimodipine

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

- Propofol

RUBILIM CR may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

- Olanzapine

RUBILIM CR may decrease the olanzapine plasma concentration.

- Felbamate

RUBILIM CR may decrease the felbamate mean clearance by up to 16 %.

- Rufinamide

RUBILIM CR may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, particularly in children, as this effect is larger in this population.

Effects of other medicines on RUBILIM CR:

Antidepressants and neuroleptics may antagonize the anti-epileptic activity of RUBILIM CR by lowering the seizure threshold. This may require RUBILIM CR dosage adjustments.

Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbitone, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of felbamate and RUBILIM CR may increase valproate serum concentration. Valproate dosage should be monitored.

Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.

Chloroquine may also lower the seizure threshold.

In case of concomitant use of RUBILIM CR and highly protein bound medicines (aspirin), valproate free serum levels may be increased.

Close monitoring of INR should be performed in case of concomitant use of vitamin K dependent factor anticoagulants (e.g. warfarin and other coumarin anticoagulants) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by RUBILIM CR.

Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

Carbapenem antibiotics (panipenem/meropenem): Decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined.

If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

- Rifampicin

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, RUBILIM CR dosage adjustment may be necessary when it is co-administered with rifampicin.

- Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease valproate plasma level when co-administered.

- Cholestyramine

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

- 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 valproate efficacy (see section 4.4). Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative medicines in women receiving hormonal contraception.

Other interactions:

Caution is advised when using RUBILIM CR in combination with newer anti-epileptics whose pharmacodynamics may not be well established. Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two medicines, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

- Quetiapine

Co-administration of RUBILIM CR and quetiapine may increase the risk of neutropenia/ leucopenia.

4.6 Fertility, pregnancy and lactation

Pregnancy:

RUBILIM CR is contraindicated in 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:

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

RUBILIM 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 RUBILIM CR:

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

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

From experience in treated epileptic mothers, the risk associated with the use of RUBILIM CR during pregnancy has been described as follows:

· Risk associated with epilepsy and anti-epileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3 %) reported in the general population. Although an increased number of children with malformations have been reported in case of multiple drug therapy, the respective part of treatments and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations.

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or anti-epileptic treatment.

Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both the mother and the foetus.

· Risk associated with sodium valproate

In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit.

In humans: cases of facial dysmorphia have been reported. A few cases of multiple malformations, particularly of the limbs have been observed. The frequency of those effects has not been yet clearly established. Nevertheless sodium valproate preferably induces neural tube defects (1 to 2 %): anencephaly, myelomeningocele and spina bifida.

· In view of the above data

If a woman plans a pregnancy, it is the opportunity of reviewing the indication for RUBILIM CR therapy.

During pregnancy, RUBILIM CR treatment should be reviewed and the risks and benefits should be carefully considered and discussed with the patient. If considered appropriate, folate supplementation should be started before pregnancy and at relevant dosage as it may minimise the risk of neural tube defects.

Monotherapy at the minimum effective daily dosage. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable.

Specialised prenatal monitoring should be instituted in order to detect the possible occurrence of neural tube defect or another malformation.

· Risk in the neonate

Cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal.

Hypofibrinogenemia is possibly associated with decrease of coagulation factors.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation:

RUBILIM CR crosses the placenta. When given to breast-feeding mothers, RUBILIM CR is excreted in breast milk.

Excretion of valproate in breast milk results in a concentration between 1 % and 10 % of maternal serum levels. Mothers taking RUBILIM CR should not breastfeed their infants (see section 4.3)

Fertility:

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using RUBILIM CR (see section 4.8).

RUBILIM CR administration may also impair fertility in men (see section 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 valproate.

It is not known with certainty if fertility would be affected by RUBILIM 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

Summary of safety profile:

Valproic acid has multiple serious adverse reactions such as hepatotoxicity, hallucinations, suicidality, psychosis, toxic epidermal necrolysis, Steven Johnson Syndrome, anaphylaxis, hyponatremia, SIADH, pancreatitis, thrombocytopenia, pancytopenia, hyperammonaemia, myelosuppression, hypothermia, aplastic anaemia, bleeding, erythema multiforme, polycystic ovarian syndrome, cerebral pseudo atrophy, encephalopathy, and coma. Abrupt discontinuation of the drug can cause withdrawal seizures.

More common reactions that have been reported in patients using valproic acid are headache, abdominal pain, somnolence, dizziness, thrombocytopenia, asthenia, nausea & vomiting, diarrhoea, dizziness, tremor, weight changes, alopecia, constipation, emotional lability, insomnia, petechiae & ecchymosis, depression, rash, nervousness, appetite changes, ALT and AST elevation, tinnitus, blurred vision, nystagmus, photosensitivity, myalgia, and dyspnoea.

Listed summary of adverse reactions

The following adverse reactions has been observed during use of Rubilim CR.

Hepatobiliary disorders

Frequent: liver injury (see section 4.1)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.1).

Gastrointestinal disorders

Frequent: nausea, vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking RUBILIM CR with or after food.

Less Frequent: pancreatitis, sometimes lethal (see section 4.4)

Nervous system disorders:

Frequent: tremor, extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Less Frequent: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Frequency unknown: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbitone or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:

Frequent: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

Frequency unknown: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:

Frequent: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Frequency unknown: hyperammonaemia* (see section 4.4.2), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur RUBILIM CR should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2). In such cases further investigations should be considered.

Endocrine disorders:

Less Frequent: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Frequency unknown: hypothyroidism (see section 4.6)

Blood and lymphatic system disorders:

Frequent: anaemia, thrombocytopenia, (see section 4.4.2)

Less Frequent: pancytopenia, leucopenia

Frequency unknown: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (RUBILIM CR has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see section 4.6).

Skin and subcutaneous tissue disorders:

Frequent: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.

Less Frequent: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Frequency unknown: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:

Frequent: dysmenorrhea

Less Frequent: amenorrhea

Frequency unknown: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:

Frequent: haemorrhage (see sections 4.4.2 and 4.6)

Less Frequent: vasculitis

Eye disorders:

Frequency unknown: diplopia

Ear and labyrinth disorders:

Frequent: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:

Frequent: urinary incontinence

Less Frequent: renal failure

Frequency unknown: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with RUBILIM CR therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:

Less Frequent: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:

Less Frequent: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with RUBILIM CR. The mechanism by which RUBILIM CR affects bone metabolism has not been identified.

Frequency unknown: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2)

Respiratory, thoracic and mediastinal disorders:

Less Frequent: pleural effusion

Investigations:

Frequency unknown: coagulation factors decreased (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)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Frequency unknown: myelodysplastic syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions 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 a coma, with muscular hypotonia, hyporeflexia, miosis and impaired respiratory function.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

Hospital management of overdose should be symptomatic: cardio-respiratory monitoring, assisted ventilation and other supportive measures are recommended. Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases.

Deaths have occurred following massive overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

Pharmacological classification: Anticonvulsants, including anti-epileptics

Sodium valproate has anticonvulsant properties. The exact mode of action is unknown. However, the most likely mode of action for valproate is potentiation of the inhibitory action

of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

5.2 Pharmacokinetic properties

Peak plasma concentrations are observed in 1 to 4 hours after sodium valproate liquid, 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 or IV administration.

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 proteins; protein binding is dose dependent and saturable. 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 is mainly excreted in urine following metabolism via glucuro-conjugation and beta-oxidation.

Sodium valproate does not increase its own degradation, neither that of other medicines such as oestrogen and progestogen containing medicines.

The elimination half-life of sodium valproate varies from approximately 8 to 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 in epilepsy is considered to be between 30 and 100 µg/ml. This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6 % and 15 % of total plasma levels.

The pharmacological (or therapeutic) effects of RUBILIM 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, trough plasma levels should be used for therapeutic monitoring.

5.3 Preclinical safety data

Reproductive and developmental toxicity

Valproate induced teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits. (see section 4.6)

Animal studies show that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose

Ethylcellulose

Silicon Dioxide

Coating

Opadry OY- S- 6705 Violet

Opadry 09B505001 Blue

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package in order to protect from light and moisture.

Keep out of reach of children.

6.5 Nature and contents of container

RUBILIM CR is packed in cold form ALU-ALU blister packs in cartons of 56, 60, 100 or 120 or 140 tablets**.**

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

P.O. Box 431

Pinetown 3600

8 REGISTRATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 April 2022

10 DATE OF REVISION OF THE TEXT