1.3.2 PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S3

RUBILIM CR 200 (Prolonged release tablets)

RUBILIM CR 300 (Prolonged release tablets)

RUBILIM CR 500 (Prolonged release tablets)

Sodium Valproate 200 mg; 300 mg or 500 mg

Sugar Free

Read all of this leaflet carefully before you start taking **RUBILIM CR**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- **RUBILIM CR** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

1. What RUBILIM CR is and what it is used for

RUBILIM CR is a prolonged release tablet which means that the active ingredient sodium valproate, is slowly released from the tablets over a period of time.

RUBILIM CR is a medicine for the treatment of epilepsy and mania.

RUBILIM CR is used in the treatment of:

- Epilepsy (fits) in adults and children
- Mania, where you may feel excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called ‘‘bipolar disorder’’.

2. What you need to know before you take RUBILIM CR

Do not take RUBILIM CR:

If you are hypersensitive (allergic) to sodium valproate or any of the other ingredients of RUBILIM CR (listed in section 6).

If you are breastfeeding your baby (see “Pregnancy and Breastfeeding”).

if you are pregnant:

For the treatment of epilepsy:

- if you or your female (girl) child are pregnant, unless there is no suitable alternative treatment.
- if you or your female (girl) child are able to have a baby, unless the conditions of the pregnancy prevention programme are met (see “Pregnancy – Important advice for women”).

For the treatment of bipolar disorder:

- if you are pregnant.
- if you are a woman able to have a baby, unless the conditions of the pregnancy prevention programme are met (see “Pregnancy – Important advice for women”).

If you have an active disease of the liver, including the following:

- if you have short or long-term (severe) hepatitis (inflammation of the liver)
- if you (or any of your close relatives) have a past history of severe hepatitis (Inflammation of the liver), especially when caused by medicines
- if you suffer from liver porphyria (a very rare metabolic disease)
- if you have been told you have a genetic problem caused by a mitochondrial

disorder (e.g. Alpers-Huttenlocher syndrome)

- if you have a known metabolic disorder, i.e. a urea cycle disorder.

If you think you may have any of these problems, or if you are in any doubt at all, consult your doctor before taking RUBILIM CR.

Warnings and precautions

Take special care with RUBILIM CR:

- **If you are a woman or female adolescent able to have a baby:**
- If you are a woman or female adolescent that is old enough to become pregnant your doctor should only treat you with RUBILIM CR if you are not pregnant and you fulfil the requirements of the pregnancy prevention programme. See “Pregnancy: Pregnancy: Important information for women”.
- If you are taking RUBILIM CR and you decide you want to start a family, talk to your doctor about this as soon as possible. Do not stop RUBILIM CR or using birth control (contraception) - until you have been able to discuss this with your doctor. You need to talk to your doctor about the risks for your baby’s health while keeping your illness under control. You and your doctor should agree on what to do with your treatment before you start trying for a baby.
- If you are pregnant, talk to your doctor immediately.
- If you develop a sudden illness, especially if it is within the first six months of treatment, and particularly if it includes repeated vomiting, extreme tiredness, abdominal pain, drowsiness, weakness, loss of appetite, upper stomach pain, nausea, jaundice (yellowing of the skin or whites of the eyes), swelling of the legs or worsening of your epilepsy or a general feeling of being unwell, YOU SHOULD TELL YOUR DOCTOR IMMEDIATELY. RUBILIM CR can affect the liver (and sometimes the pancreas) in a very small number of patients.
- If you have (SLE) systemic lupus erythematosus (a rare disease of the immune system which affects skin, bones, joints and internal organs)
- If you have been told that you have any metabolic disorders, particularly hereditary enzyme deficiency disorders such as a urea cycle disorder where too much ammonia builds up in the body.
- If you have kidney problems. Your doctor may want to monitor the level of RUBILIM CR in your body or give you a lower dose.

- If you put on weight as your appetite may be increased. Talk to your doctor about how this will affect you.
- If you or your child have diabetes, RUBILIM CR may affect the results of urine tests.
- If at any time you have thoughts of harming or killing yourself, immediately contact
- your doctor.
- If you drink alcohol. Alcohol intake is not recommended during treatment with RUBILIM CR.
- If you have been told that you have carnitine palmitoyl transferase type II deficiency.
- If you have been told that there is a genetic problem caused by a mitochondrial disorder in your family.

Your doctor or your child's doctor may wish to do blood tests before you or your child start taking RUBILIM CR and during your treatment.

RUBILIM CR should only be used in adult males who plan to father a child if alternative treatment options are not suitable.

RUBILIM CR should not be used in children under the age of 18 years for the treatment of mania associated with bipolar disorders.

Taking with food and drink

Alcohol intake is not recommended during treatment.

Other medicines and RUBILIM CR

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

This is because RUBILIM CR can affect the way some other medicines work. Also some medicines can affect the way RUBILIM CR works.

The following medicines can increase the chance of you getting side effects, when taken with RUBILIM CR:

- Some medicines used for pain and inflammation (salicylates) such as aspirin.

- Some other medicines used to treat fits (epilepsy) – phenobarbital, primidone, phenytoin, carbamazepine, topiramate, acetazolamide, lamotrigine, rufinamide and felbamate.
- Medicines which are used to treat schizophrenia or bipolar disorder containing quetiapine.

RUBILIM CR may increase the effect of the following medicines:

- Medicines used for thinning the blood (such as warfarin)
- Medicines used for HIV infection containing zidovudine
- Medicines for depression such as citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, venlafaxine, aripiprazole
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Propofol, an anaesthetic
- Nimodipine

The following medicines can affect the way RUBILIM CR works:

- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine - used for stomach ulcers
- Cholestyramine used to lower blood fat (cholesterol) levels
- Some medicines used for infections (antibiotics) such as rifampicin and erythromycin
- Lopinavir and ritonavir – used for HIV treatment
- Estrogen-containing products (including some birth control pills)
- In particular, tell your doctor or nurse if you are taking any of the following medicines: Carbapenem medicines (antibiotics used to treat bacterial infections). The combination of valproic acid and carbapenems should be avoided because it may decrease the effect of sodium valproate.

Pregnancy, breast-feeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

Pregnancy

You should not use RUBILIM CR if you are pregnant or breastfeeding your baby unless nothing else works for you.

If you are a woman able to have a baby, you must not take RUBILIM CR unless you use an effective method of birth control (contraception) during your entire treatment with RUBILIM CR.

Do not stop taking RUBILIM CR or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

Important advice for women:

If you are pregnant, you must not use RUBILIM CR, unless your doctor has determined there is no suitable alternative treatment.

If you are able to have a baby, you must not use RUBILIM CR unless the conditions of the pregnancy prevention programme are met.

RUBILIM CR can be harmful to unborn children when taken by a woman during pregnancy. RUBILIM CR can cause serious birth defects and can affect the way in which the child develops as it grows.

The conditions of the pregnancy prevention programme require that before RUBILIM CR is prescribed for you:

- your doctor must explain what might happen to your baby if you become pregnant while taking RUBILIM CR. You need to ensure you understand these risks.
- you will be asked to perform a pregnancy test before starting RUBILIM CR, or thereafter if needed. This is to make sure you are not pregnant.
- effective birth control (contraception) will be recommended for you to avoid becoming pregnant while taking RUBILIM CR.
- your doctor will assess your understanding of contraception and the need for contraception without interruption during the entire duration of treatment with RUBILIM CR.

- your doctor will review your treatment regularly (at least once a year).
- your doctor will ask you to read and sign an “Annual Risk Acknowledgement Form” to make sure you are well aware and have understood all the risks related to the use of RUBILIM CR during pregnancy and are aware and understand the recommendations to avoid becoming pregnant.
- a Patient Guide will be given to you by your doctor. Make sure you read the Patient Guide that you will receive from your doctor. you will also receive a Patient Card from your pharmacist to remind you of the risks of using RUBILIM CR in pregnancy.
- your doctor will explain what to do if you decide later that you want to have a baby. If you are planning a baby, you must first discuss this with your doctor. You must not stop taking RUBILIM CR or interrupt your method of contraception until you have discussed this with your doctor.

Please choose the situations which apply to you and read the descriptions that follow:

□ I AM STARTING TREATMENT WITH RUBILIM CR (First Prescription)

□ I AM TAKING RUBILIM CR AND I AM NOT PLANNING TO HAVE A BABY

□ I AM TAKING RUBILIM CR AND I AM PLANNING TO HAVE A BABY

□ I AM PREGNANT AND I AM TAKING RUBILIM CR

I AM STARTING TREATMENT WITH RUBILIM CR (First Prescription):

- If this is the first time you have been prescribed RUBILIM CR, your doctor will have explained the risks to an unborn child if you become pregnant.
- If you are able to have a baby or once you are able to have a baby, you will need to make sure that you use an effective method of birth control (contraception) throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.
- Pregnancy must be excluded before start of treatment with RUBILIM CR through the result of a pregnancy (blood) test, to be confirmed by your doctor.
- You must discuss appropriate methods of birth control (contraception) with your doctor.

- You must make sure you are using an effective method of birth control (contraception) during your entire treatment. You must get regular (at least annual) appointments with a medical practitioner experienced in the management of epilepsy or bipolar disorder.
- Tell your doctor at once if you are pregnant or think you might be pregnant.
- Tell your doctor if you plan to become pregnant.

I AM TAKING RUBILIM CR AND I AM NOT PLANNING TO HAVE A BABY:

- If you are continuing treatment with RUBILIM CR and you do not plan to have a baby, make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with RUBILIM CR. Talk to your doctor or family planning clinic if you need advice on contraception.
- Make sure you are using an effective method of contraception during your entire treatment.
- You must get regular (at least annual) appointments with a medical practitioner experienced in the management of epilepsy or bipolar disorder.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.
- Tell your doctor if you plan to become pregnant.

I AM TAKING RUBILIM CR AND I AM PLANNING TO HAVE A BABY:

If you are on treatment with RUBILIM CR and planning to have a baby, first schedule an appointment with your doctor. You should talk to your doctor long enough before you become pregnant so that you and your doctor can put several actions in place to ensure that your pregnancy goes as smoothly as possible, and any risks to you and your unborn child are reduced as much as possible. Your doctor may prescribe another medicine for your epilepsy which may have less risk for your baby. Do not stop taking RUBILIM CR or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you on when you can stop your contraception.

Babies born to mothers who have been on RUBILIM CR are at serious risk of birth defects and problems with development, which can be seriously debilitating.

Your doctor may want to adjust your treatment and/or prescribe dietary supplements of folic acid.

Folic acid may lower the risk of spina bifida (a birth defect) and early miscarriage. However, it is unlikely that folic acid will reduce the risk of birth defects associated with RUBILIM CR use.

You must not stop taking RUBILIM CR unless your doctor agrees, as there are severe risks to yourself and your developing baby if your epilepsy is not controlled.

If you are pregnant, or think you might be pregnant, see your doctor immediately.

I AM PREGNANT AND I AM TAKING RUBILIM CR:

Women should not become pregnant while receiving RUBILIM CR. You should use an effective method of birth control (contraception) and consult your doctor before planning pregnancy.

RUBILIM CR has no effect on the efficacy of your oral contraceptive pill.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Do not stop taking RUBILIM CR unless your doctor tells you to, as your condition may become worse.

During pregnancy, should a mother suffer from a serious type of seizure, where the oxygen supply to her and her unborn baby may be cut off, the risk of death to the mother and unborn child is increased. Your doctor will advise you further.

Make sure you are referred to a medical practitioner experienced in the treatment of epilepsy or bipolar disorder to re-assess your treatment options.

You must get thorough counselling on the risks of RUBILIM CR during pregnancy, including malformations and developmental effects in children.

Make sure you are referred to a medical practitioner for prenatal monitoring in order to detect possible occurrences of malformations.

The risks of RUBILIM CR when taken during pregnancy:

- Babies born to mothers who are taking RUBILIM CR, are at serious risk of birth defects and problems with development which can be seriously debilitating.
- It is known that in women who take RUBILIM CR, around 10 babies in every 100 will have birth defects, as compared to 2 – 3 babies in every 100 born to women who do not have epilepsy.
- These birth defects to your developing baby include spina bifida (condition where bones of the spine are not properly developed), craniofacial defects (face and skull malformations), malformation of the limbs, heart, kidney and sexual organ malformations, hypospadias (malformation of the urethra) and multiple anomalies involving various body systems.
- Children born to mothers who take RUBILIM CR during pregnancy, may have impaired physical and mental development or autistic disorders.
- It is estimated that up to 30 to 40 % of preschool children whose mothers took RUBILIM CR during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, less intellectually able than other children, and have difficulty with language and memory.
- It is therefore essential that you discuss your treatment with your doctor if you are thinking of becoming pregnant or tell your doctor as soon as you know you are pregnant.
- Your doctor may want to adjust your treatment and/or prescribe dietary supplements of folate.
- You must not stop taking RUBILIM CR unless your doctor agrees, as there are severe risks to yourself and your developing baby if you have uncontrolled epilepsy.

Newborn babies of mothers who took RUBILIM CR during pregnancy may have:

- blood clotting problems (blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- hypoglycaemia (low blood sugar levels).
- hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).

- withdrawal syndrome (agitation, irritability, hyper-excitability, jitteriness, hyperkinesia (muscle spasm), muscle problems, tremor, convulsions and feeding problems); when taken during the last trimester of pregnancy.

Breastfeeding:

RUBILIM CR passes into the breast milk, You should not breastfeed your baby if you are using RUBILIM CR

Fertility:

RUBILIM CR can cause infertility in both men and women that may not always be reversible.

Driving and using machines

You may feel sleepy when taking RUBILIM CR. If this happens to you, do not drive or use any tools or machines.

3. How to take RUBILIM CR

Do not share medicines prescribed for you with any other person. Always take RUBILIM CR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. RUBILIM CR treatment must be started and supervised by a doctor specialised in the treatment of epilepsy or bipolar disorders.

Taking this medicine

- Your doctor will decide how much RUBILIM CR to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- Take RUBILIM CR with or after food. This will help to stop the feelings of sickness that may happen after taking RUBILIM CR.
- Do not crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine

- This medicine can be taken once or twice daily

How much to take:

Dosage for Mania:

The daily dosage should be established and controlled individually by your doctor.

Initial dose: The recommended initial daily dose is 1000mg.

Mean daily dose: The recommended daily doses usually range between 1000 mg and 2000 mg.

Dosage for Epilepsy:

Adults (including the elderly)

- The starting dose is 600mg daily. Your doctor will gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is generally between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms

- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child’s illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child’s illness

Children under 20 kilograms

The usual dose of RUBILIM CR is based on the child's weight as an amount of RUBILIM CR for each kg of bodyweight. The usual dose ls 20 mg for each kg of body weight. This quantity should be divided and given in 2 separate doses e.g. half in the morning and half in the evening.

Patients with kidney problems

- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)

- You or your child may be taking other medicines for epilepsy at the same time as RUBILIM CR. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of RUBILIM CR by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more RUBILIM CR than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.
Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen; feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss, low blood pressure and unusual or inappropriate behaviour.
Taking too much RUBILIM CR may result in too much sodium in your blood (hypernatremia).

If you forget to take RUBILIM CR

If you forget to take a dose, take it as soon as you remember. However, if is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

RUBILIM CR can have side effects.

Not all side effects reported for RUBILIM CR are included in this leaflet. Should your

general health worsen or if you experience any untoward effects while taking this medicine,

please consult your doctor, pharmacist or other healthcare professional for advice.

If you get any of the following side effects, stop taking RUBILIM CR and tell your doctor immediately, or go to the casualty department at your nearest hospital:

• Allergic reactions (including swelling of the face, eyelids, lips, tongue, throat; difficulty in breathing and swallowing).

These are all very serious side effects. If you have them, you may have had a serious reaction to RUBILIM CR. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- changes in the amount of ammonia in the blood (symptoms are vomiting, problems with balance, feeling less alert);
- liver problems (being nauseous and vomiting many times, being very tired, sleepy and weak, stomach pain, yellowing of the skin or whites of the eye);
- inflammation of the pancreas (acute abdominal pain); chest pain; shortness of breath; see also Take special care with RUBILIM CR above.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

The following side effects occur frequently:

Headache; sleep disorders; clumsiness or unsteadiness; trembling of hands and arms; nervousness; changing moods; blurred vision; ringing in ears; deafness, dizziness; flu; abdominal or stomach pain; heartburn; nausea and vomiting; diarrhoea; skin rash; hair loss or thinning of hair; back pain; change in menstrual periods; lack or loss of strength, mental confusion, aggression, convulsion, memory problems, becoming unreactive, bedwetting.

The following side effects occur less frequently:

Unusual bleeding or bruising; abnormal dreams; anxiety; feeling sad; irritability; pain in joints; cough; constipation; rolling of the eyes; dry eyes; spots before the eyes; ear infection; ear

pain; runny nose; dental pain; bloated full feeling; muscle pains or stiffness; fatigue, weight gain or loss, learning disorder, coma, loss of muscle control, brittle bones and fractures, shortness of breath and chest pain, blood clotting problems.

Side effects occurring at unknown frequency:

RUBILIM CR can change levels of liver enzymes, salts or sugars shown up on blood and urine tests. Various birth defects and developmental delays have been reported in babies born of women taking RUBILIM CR during pregnancy (see Pregnancy and breastfeeding for details and advice).

If you notice any side effects not mentioned in this leaflet please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects 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. By reporting side effects, you can help provide more information on the safety of **RUBILIM CR**

5. How to store RUBILIM CR

Store all medicines out of reach of children.

Store at or below 25^0 C

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

6. Contents of the pack and other information

What **RUBILIM CR** contains

The active substance is sodium valproate

The other ingredients are:

Tablet Core

- Hypromellose
- Ethylcellulose
- Silicon Dioxide

Coating

- Opadry OY- S- 6705 Violet
- Opadry 09B505001 Blue

What **RUBILIM CR** looks like and contents of the pack

RUBILIM CR 200: film coated, oblonged shaped and violet coloured prolonged release tablet

RUBILIM CR 200: film coated, oblonged shaped and blue coloured prolonged release tablet.

RUBILIM CR 200: film coated, oblonged shaped and violet coloured prolonged release ablet.

Tablets are 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.

Holder of Certificate of Registration

Ruby Pharmaceuticals (PTY) LTD

P.O. Box 431

Pinetown 3600

This leaflet was last revised in