Professional information for VARIPAN CO

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

VARIPAN CO 500 mg/8 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol and 8 mg codeine phosphate.

Sugar free.

Preservative:

Potassium sorbate 0,1 % *m/m.*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white capsule-shaped tablet with a half score on both sides and embossed ‘P’ and ‘C’ on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VARIPAN CO is indicated for the relief of mild to moderate pain and for the reduction of temperature in febrile conditions.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults:

One or two tablets every four to six hours.

Children over 12 years:

One tablet every four to six hours.

Children 6 to 12 years:

Half to one tablet every six hours.

Do not exceed an adult dose of 8 tablets per day.

Do not use continuously for longer than five (5) days without consulting your doctor.

Paediatric population

The safety and efficacy of VARIPAN CO has not been established in children under 6 years of age.

Method of administration

For oral use.

4.3 Contraindications

- VARIPAN CO is contraindicated in patients with a known hypersensitivity to paracetamol, codeine phosphate or to any of the excipients listed in section 6.1.
- Respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- Acute asthma attacks, severe bronchial asthma, hypercarbia and chronic respiratory impairment or disease.
- Drug abuse or dependence, including acute alcoholism.
- Biliary tract disease or after operations on the biliary tract.
- Hepatic function impairment, including hepatic disease or viral hepatitis.
- Renal function impairment, including phenylketonuria, urethral stricture or recent urinary tract surgery.
- Acute pancreatitis.

- Depleted blood volume, circulatory shock.
- Cardiac arrhythmias.
- Addison's disease.
- History of convulsions.
- Acute abdominal conditions, including diarrhoea, severe inflammatory bowel disease or recent gastrointestinal tract surgery.
- Emotional instability.
- Gallbladder disease or gallstones.
- Prostatic hypertrophy or obstruction.
- Kyphoscoliosis.
- Hypothyroidism.
- Head injury or pre-existing increased intracranial pressure or intracranial lesions.
- Heart failure secondary to lung disease.
- In patients for whom it is known that they are CYP2D6 ultra-rapid metabolisers (see section 4.4).
- In all paediatric patients (0 –18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.5).

4.4 Special warnings and precautions for use

VARIPAN CO contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

- VARIPAN CO should be given with extreme caution in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

- Dosages in excess of those recommended may cause severe liver damage.
- Consult your doctor if no relief is obtained with the recommended dosage.
- Do not use continuously for longer than 10 days without consulting your doctor.
- VARIPAN CO should be used with caution in patients with myasthenia gravis.
- The dosage should be reduced in the elderly and debilitated patients.
- VARIPAN CO should be used with caution in patients that are in a state of shock.
- Exceeding the prescribed dose, together with prolonged and continuous use of VARIPAN CO, may lead to dependency and addiction. There is also an increased risk of addiction in patients with a personal or family history of substance abuse or mental health disorders.
- The administration of VARIPAN CO during labour may cause respiratory depression in the newborn infant.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, treatment with VARIPAN CO must immediately be discontinued and appropriate treatment instituted.

Central nervous system (CNS) depressants

Concomitant use of VARIPAN CO and sedating medicines such as benzodiazepines or related medicines, may result in sedation, respiratory depression, coma and death. The use of VARIPAN CO concurrently with other central nervous system depressants, such as alcohol, anaesthetics, phenothiazines and tricyclic antidepressants, may cause additive CNS depressant effects (see section 4.5). Because of these risks, concomitant prescribing with these sedating medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe VARIPAN CO concomitantly with sedating medicines, the lowest effective dose

of VARIPAN CO should be used, and the duration of the concomitant treatment should be as short as possible.

The patients should be monitored closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

CYP2D6 metabolism

Codeine, as in VARIPAN CO, is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme, an adequate analgesic effect may not be obtained.

However, if the patient is an ultra-rapid metaboliser of the CYP2D6 enzyme, there is a risk of developing side effects of opioid toxicity even within the recommended dosage range. Patients who are CYP2D6 ultra-rapid metabolisers may convert codeine into morphine rapidly, resulting in higher than expected serum morphine levels (see section 4.3).

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Paediatric population

Children under 6 years

VARIPAN CO is not suitable for children under the age of 6 years (see section 4.2).

Post-operative use in children

VARIPAN CO should not be given post-operatively to children under 18 years after tonsillectomy

and/or adenoidectomy for obstructive sleep apnoea, as it may lead to rare, but life-threatening adverse events including death (see section 4.3).

Children with compromised respiratory function

VARIPAN CO is not recommended for use in children in whom respiratory function may be compromised, including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

Administration of pethidine and possibly other opioid analgesics such as codeine in VARIPAN CO, to patients taking a MAOI has been associated with very severe and sometimes fatal reactions (see section 4.3).

CNS depression or excitation may occur if VARIPAN CO is given to patients receiving MAOIs, or within 14 days of stopping treatment with them.

Central nervous system (CNS) depressants

The concomitant use of opioids, such as VARIPAN CO, with sedating medicines (e.g. benzodiazepines or related substances), including alcohol, increases the risk of sedation, respiratory depression, coma and death because of the additive CNS depressant effect. The dose of VARIPAN CO and the duration of concomitant use should be limited (see section 4.4).

Anticoagulants

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol (as in VARIPAN CO) with increased risk of bleeding; occasional doses have no significant effect.

Anticoagulant dosage adjustment based on increased monitoring of prothrombin time may be necessary when chronic, high-dose paracetamol therapy is initiated or discontinued.

Hepatotoxic medicines

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes. The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing medicines such as carbamazepine, phenobarbital (phenobarbitone), phenytoin, primidone or rifampicin.

Probenecid

Excretion of paracetamol may be reduced and plasma concentrations increased when VARIPAN CO is given with probenecid.

Isoniazid

Concomitant use of VARIPAN CO with isoniazid may cause hepatotoxicity.

Antidiarrhoeal and antiperistaltic medicines

Concurrent use of VARIPAN CO with antidiarrhoeal and antiperistaltic medicines, such as loperamide and kaolin, may increase the risk of severe constipation.

Antimuscarinic medicines

Concomitant use of antimuscarinics or medicines with antimuscarinic action may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Neuromuscular blocking medicines

The respiratory depressant effects caused by neuromuscular blocking medicines may be additive to the central respiratory depressant effects of VARIPAN CO.

Antihypertensive medicines

The hypotensive effects of antihypertensive medicines, including diuretics, may be potentiated when used concurrently with VARIPAN CO.

Hydroxyzine

Concurrent use of hydroxyzine with VARIPAN CO may result in increased analgesia as well as increased CNS depressant and hypotensive effects.

Cimetidine

Cimetidine inhibits the metabolism of opioid analgesics, as in VARIPAN CO, resulting in increased plasma concentrations.

Naloxone

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics, as in VARIPAN CO. Naltrexone also blocks the therapeutic effect of opioids.

Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or other salicylates

Chronic high-dose administration of the combined analgesics increases the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal disease and cancer of the kidney or urinary bladder.

CYP3A4 inducers

CYP3A4 inducers (such as phenytoin and rifampicin) may increase methadone metabolism and may precipitate withdrawal symptoms in patients being treated for opioid dependence.

Zidovudine

Concurrent use should be avoided because the toxicity of either or both of these medicines may be

potentiated.

Other medicines

The speed of absorption of paracetamol, as in VARIPAN CO, may be increased by metoclopramide or domperidone, and absorption reduced by colestyramine.

VARIPAN CO may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

VARIPAN CO may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Patients receiving other narcotic analgesics, antitussive medicines, antihistamines, antipsychotics or antianxiety medicines concomitantly with VARIPAN CO may exhibit additive CNS depression.

Laboratory tests

VARIPAN CO may interfere with a number of laboratory tests, including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. VARIPAN CO may also interfere with gastric emptying studies as they delay gastric emptying, and with hepatobiliary imaging using technetium Tc99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increases biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of VARIPAN CO in pregnancy has not been established.

Administration of codeine during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding

The safety of VARIPAN CO in lactation has not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

VARIPAN CO may cause side effects, such as somnolence and dizziness (see section 4.8) and therefore affect the ability to drive a vehicle or use machinery. This applies particularly in conjunction with other psychotropic medicines, including alcohol (see section 4.5). Caution is advised before driving a vehicle or operating machinery until the effects of VARIPAN CO are known.

4.8 Undesirable effects

List of adverse reactions

The following adverse reactions have been reported with codeine phosphate and paracetamol combination, such as VARIPAN CO:

Blood and lymphatic system disorders

Frequency unknown: agranulocytosis, thrombocytopenia.

Immune system disorders

Frequency unknown: hypersensitivity/allergic reactions, comprising erythema, rash, pruritus, urticaria, angioedema, dyspnoea, and anaphylactic reactions (including shock).

Psychiatric disorders

Frequency unknown: medicine dependence (see section 4.4), change in mood (dysphoria, euphoria), restlessness, confusion.

Nervous system disorders

Frequency unknown: dizziness, light-headedness, somnolence, raised intracranial pressure, deepening coma, seizure, headache.

Eye disorders

Frequency unknown: miosis.

Ear and labyrinth disorders

Frequency unknown: vertigo.

Cardiac disorders

Frequency unknown: bradycardia, palpitations.

Vascular disorders

Frequency unknown: hypotension, facial flushing, orthostatic hypotension, circulatory failure.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: respiratory depression.

Gastrointestinal disorders

Less frequent: acute pancreatitis, increased risk of abdominal pain.

Frequency unknown: constipation, nausea, vomiting, dry mouth.

Hepatobiliary disorders

Frequency unknown: ureteric or biliary spasm.

Skin and subcutaneous tissue disorders

Less frequent: serious skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), fixed drug eruption, allergic reactions (hypersensitivity) including skin rash have been reported.

Musculoskeletal and connective tissue disorders

Frequency unknown: muscle rigidity.

Renal and urinary disorders

Frequency unknown: urinary retention, micturition, sweating, anti-diuretic effect.

General disorders and administration site conditions

Less frequent: medicine withdrawal syndrome.

Frequency unknown: hypothermia.

The following adverse reactions have been reported for codeine:

Metabolism and nutrition disorders

Less frequent: loss of appetite.

Psychiatric disorders

Less frequent: paradoxical reaction (restlessness), false sense of well-being, hallucinations, mental depression, insomnia, confusion.

Nervous system disorders

Frequent: drowsiness.

Less frequent: dizziness, convulsions, headache, trembling or uncontrolled muscle

movements.

Frequency unknown: light-headedness.

Eye disorders

Less frequent: blurred or double vision.

Ear and labyrinth disorders

Frequency unknown: ringing or buzzing in the ears.

Cardiac disorders

Less frequent: irregular heart rhythm.

Frequency unknown: increased blood pressure.

Vascular disorders

Less frequent: hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: atelectasis, bronchospastic allergic reaction, allergic laryngeal oedema, allergic laryngospasm, respiratory depression.

Gastrointestinal disorders

Frequent: constipation.

Less frequent: paralytic ileus, dry mouth, gastrointestinal irritation, nausea.

Hepatobiliary disorders

Less frequent: biliary spasm.

Frequency unknown: hepatotoxicity.

Skin and subcutaneous tissue disorders

Less frequent: allergic reaction (skin rash).

Musculoskeletal and connective tissue disorders

Less frequent: muscle rigidity.

Renal and urinary disorders

Less frequent: antidiuretic effect, urethral spasm.

Frequency unknown: urinary retention.

General disorders and administration site conditions

Less frequent: general feeling of discomfort, unusual tiredness or weakness.

Description of selected adverse reactions

Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is stopped. Prolonged use of a painkiller for headaches can make them worse.

Post-marketing experience

Gastrointestinal disorders

Increased risk of abdominal pain, including pancreatitis.

The following adverse reactions have been reported for paracetamol:

Blood and lymphatic system disorders

Less frequent: agranulocytosis, anaemia, thrombocytopenia.

Hepatobiliary disorders

Less frequent: hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: allergic dermatitis.

Renal and urinary disorders

Less frequent: renal colic, renal failure, sterile pyuria.

Post-marketing experience

Skin and subcutaneous disorders

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VARIPAN CO is important. It allows continued monitoring of the benefit/risk balance of VARIPAN CO. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs and symptoms

Codeine phosphate

Symptoms include cold, clammy skin, confusion, severe dizziness, severe drowsiness, low blood pressure, severe nervousness or restlessness, pinpoint pupils of eyes, slow heartbeat, slow or troubled breathing, unconsciousness and severe weakness.

Paracetamol

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not affect the potential seriousness of the overdose.

Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenise activity, increased serum bilirubin concentration and prolongation of the prothrombin time.
Liver damage may lead to encephalopathy, coma and death.
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Codeine phosphate

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Treatment of respiratory depression or other potentially life-threatening adverse effects must take precedence. The specific antagonist, naloxone hydrochloride, is used to counteract severe respiratory depression.

Paracetamol

Prompt treatment is essential. In the event of an overdose, consult a doctor immediately. A delay may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.
Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses

(greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomes such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Treatment of paracetamol overdose

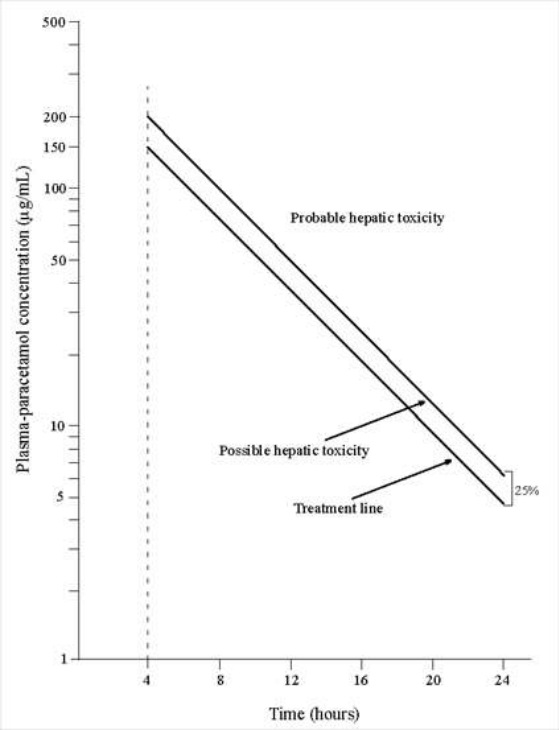
***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of the overdose, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

An initial dose of 150 mg/kg *N*-acetylcysteine in 200 mL dextrose injection given intravenously over 15 minutes, followed by infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours.

The volume of the intravenous fluid should be modified for children.

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdose. Levels done before four hours, may be misleading unless high. Patients at risk of liver damage and hence requiring continued treatment with *N*-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871–6).

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue *N*-acetylcysteine treatment with 100 mg/kg intravenously over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least ninety-six hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations.

Pharmacotherapeutic group: Paracetamol, combinations excl. Psycholeptics.

ATC code: N02B E51.

Mechanism of action

Paracetamol has analgesic and antipyretic actions.

Codeine phosphate is an analgesic of the opioid class. Opioid analgesics bind with stereospecific receptors at many sites within the CNS to alter processes affecting both the perception of pain and the emotional response to it. It has been hypothesised that alterations in release of various neurotransmitters from afferent nerves sensitive to painful stimuli may be partially responsible for the analgesic effect.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ-opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Codeine

Absorption:

Codeine and its salts are absorbed from the gastrointestinal tract. Ingestion of codeine phosphate produces peak plasma codeine concentrations in about one hour.

Distribution:

Codeine is not extensively bound to plasma proteins and is widely distributed.

Biotransformation:

Codeine is metabolised by *O*- and *N*-demethylation in the liver to morphine, norcodeine and other metabolites including normorphine and hydrocodone.

Elimination:

Codeine and its metabolites are excreted almost entirely by the kidneys, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours after an oral

dose.

Paracetamol

Absorption:

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses.

Distribution:

Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations.

Biotransformation:

Paracetamol is metabolised predominantly in the liver mainly to the glucuronide and sulphate conjugates. A minor hydroxylated metabolite (*N*-acetyl-p-benzoquinoneimine) is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate following paracetamol overdosage and cause tissue damage.

Elimination:

Paracetamol is excreted in the urine. Less than 5 % is excreted as unchanged paracetamol. The elimination half-life of paracetamol varies from about 1 to 3 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Potassium sorbate

Povidone K30

Pregelatinised starch

Purified talc

Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in airtight containers.

Protect from light.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Ten (10) tablets packed in Aluminium/PVC blister strips. Each outer carton contains 3 blisters strips.

Pack size: 30.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville 7551

Tel: 087 551 3245

8. REGISTRATION NUMBER

37/2.8/0261

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 April 2009

10. DATE OF REVISION OF THE TEXT

25 July 2025