PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

PARAFENGEN, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains paracetamol 500 mg and ibuprofen 150 mg.

Contains sugar (lactose monohydrate) 3,81 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White, capsule shaped, film-coated tablets with break-line on one side and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PARAFENGEN, film-coated tablets are indicated for the relief of headache from musculoskeletal origin, feverishness, muscular, menstrual and dental pain.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE

Use the lowest effective dose for the shortest possible duration of treatment.

PARAFENGEN should not be used for more than 10 days unless on medical advice, in which case the patient should be regards to efficacy, risk factors and ongoing need for treatment.

Adults and children over 12 years of age: The usual dosage is 1 to 2 tablets taken every 6 hours, as required, up to a maximum of 8 tablets in 24 hours.

Paediatric population

Children under 12 years of age: PARAFENGEN is not recommended for children under 12 years of age.

Method of administration

Tablets must be taken with food or after meals with sufficient water.

4.3 Contraindications

- Hypersensitivity to paracetamol, ibuprofen, aspirin or other NSAIDs or to any of the excipients (see section 6.1).
- Active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatoxicity (due to the paracetamol component) (see section 4.5).
- Asthma, bronchospasm, urticaria, or allergic-type reactions after taking aspirin, ibuprofen or other NSAIDs (see section 4.4).
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including PARAFENGEN.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Pregnancy or in patients planning to become pregnant and during breastfeeding (see section 4.6).
- Impaired kidney function, impaired liver function.
- Heart failure or cardiovascular disease.
- Patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).
- Patients receiving coumarin anticoagulants (see section 4.5).
- Bleeding disorders.

4.4 Special warnings and precautions for use

This product 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.

PARAFENGEN should not be taken with other products containing ibuprofen, paracetamol, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction (see section 4.5).

Use in older patients

No adjustment in the labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than 10 days should consult their doctor to monitor their condition although no reduction in the recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medicines. The elderly have an increased frequency of adverse reactions to NSAIDSs including PARAFENGEN, especially heart failure, gastrointestinal perforation, ulceration and bleeding (PUBs) and renal impairment which may be fatal (see section 4.3).

Haematological effects

Blood dyscrasias have been reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation defects

Ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy. PARAFENGEN use is contraindicated in patients taking coumarin anticoagulants as well as patients with bleeding disorders (see section 4.3).

Gastrointestinal events

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of PARAFENGEN, in patients with a history of ulcers, and the elderly. When

gastrointestinal bleeding or ulceration occurs in patients receiving PARAFENGEN, treatment with PARAFENGEN should be stopped. PARAFENGEN should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when this product is used at the prescribed dose for a few days.

PARAFENGEN should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or a history of peptic ulcers since their condition may be exacerbated. It is contraindicated in patients with active gastrointestinal bleeding and in those with peptic ulcers or other stomach disorders (see section 4.3).

This product should be discontinued if there is any evidence of gastrointestinal bleeding. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular thrombotic events

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with PARAFENGEN after careful consideration.

Non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur. PARAFENGEN use is contraindicated in patients with existing cardiovascular disease (see section 4.3).

Hypertension

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with PARAFENGEN therapy. In view of the PARAFENGEN inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing PARAFENGEN to patients with hypertension. Blood pressure should be monitored closely during initiation of treatment with PARAFENGEN and at regular intervals thereafter.

Hepatic effects

Dosages of PARAFENGEN in excess of recommended may cause severe liver damage.

Elevations of one or more liver function tests may occur with NSAID use. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST can occur. Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abnormal tenderness in the right upper quadrant and flu-like symptoms). PARAFENGEN use is contraindicated in hepatic impairment (see section 4.3).

Combination use of ACE inhibitors or angiotensin receptor antagonist, anti-inflammatory medicines and thiazide diuretics

The use of an ACE inhibiting medicine (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID or COX-2 inhibitor) and thiazide diuretics at the same time increases the risk of renal impairment (see section 4.5). This includes use in fixed-combination products containing more than one class of medicine. Combined use of these medicines should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of medicines from these three classes should be used with caution particularly in elderly patients.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. PARAFENGEN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Pre-existing asthma

Products containing ibuprofen should not be administered to patients with aspirin sensitive asthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

Aseptic meningitis

For products containing ibuprofen aseptic meningitis has been reported, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Masking signs of infection

Ibuprofen may mask the usual signs of infection by reducing fever.

Potential laboratory test interferences

Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Blood tests

Paracetamol at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose meters. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

Urine tests

Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding several hours before and during the collection of the urine specimen.

Special precautions

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

PARAFENGEN contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PARAFENGEN.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Paracetamol: Do not use PARAFENGEN with products containing paracetamol. The combination can result in an overdose of paracetamol, causing severe liver damage (see section 4.4).

NSAIDs: The use of two or more NSAIDs concomitantly could result in an increase in side effects.

Paracetamol

The following interactions have been noted:

- anticoagulant medicines (e.g. warfarin): dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- anti-epileptic medicines: the likelihood of toxicity may be increased by the concomitant use of enzyme inducing medicines.
- paracetamol absorption is increased by medicines that increase gastric emptying, e.g. metoclopramide.
- paracetamol absorption is decreased by medicines that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.
- paracetamol may increase chloramphenicol plasma concentrations.

- hepatotoxic medicines or medicines that induce liver microsomal enzymes such as alcohol and anticonvulsant medicines: the risk of paracetamol toxicity may be increased in patients receiving these medicines.
- probenecid: may affect paracetamol excretion and plasma concentrations.
- cholestiramine: reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- isoniazid alone or combined with other medicines for tuberculosis: in patients receiving these medicines severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported.
- zidovudine and co-trimoxazole: severe hepatotoxicity have occurred after use of paracetamol in patients taking these medicines.

Ibuprofen

The following interactions have been noted:

- anticoagulants, including warfarin – ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- lithium: ibuprofen may decrease renal clearance and increase plasma concentration of lithium.
- ACE inhibitors, beta-blockers and diuretics: ibuprofen may reduce the anti- hypertensive effect of these medicines and may cause natriuresis and hyperkalaemia in patients using these medicines. Concomitant use also increases the risk of renal impairment (see section 4.4).
- methotrexate: ibuprofen reduces methotrexate clearance.
- cardiac glycosides: ibuprofen may increase the plasma levels of these medicines.
- corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs) with concomitant use of oral corticosteroids.
- zidovudine: ibuprofen may prolong bleeding time in patients treated with this medicine.

- probenecid, antidiabetic medicine and phenytoin: these medicines may interact with ibuprofen.
- anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

PARAFENGEN should be avoided during pregnancy and in patients planning to become pregnant (see section 4.3).

Regular use of NSAIDs, such as PARAFENGEN, during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

Breastfeeding

PARAFENGEN should not be used during breastfeeding.

Fertility

Reversible infertility has been reported in women on long-term NSAIDs.

4.7 Effects on ability to drive and use machines

PARAFENGEN may be associated with dizziness, fatigue and headache (see section 4.8). Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects

a. Summary of the safety profile

Side effects of paracetamol are less frequent and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe sometimes fatal liver damage and less frequently, acute renal tubular necrosis. The most commonly observed adverse events are gastrointestinal in nature.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequency unknown	Agranulocytosis, thrombocytopenia, neutropenia, leucopenia, pancytopenia.
Immune system disorders	Frequency unknown	Allergic reactions such as skin rash, itching, swelling of the face or breathing difficulties.
Psychiatric disorders	Frequency unknown	Depression.
Nervous system disorders	Frequency unknown	Dizziness, fatigue, headache, nervousness, drowsiness, insomnia, aseptic meningitis.
Eye disorders	Frequency unknown	Blurred vision and other ocular reactions. Photosensitivity
Ear and labyrinth disorders	Frequency unknown	Tinnitus.
Cardiac disorders	Frequent	Cardiac failure, oedema, hypertension.
	Frequency unknown	Myocardial infarct, stroke.
Gastrointestinal disorders	Frequent	Gastrointestinal bleeding, dyspepsia, heartburn, nausea, loss of appetite, abdominal pain, diarrhoea,

MedDRA system organ class	Frequency	Adverse reactions
		peptic ulcers, perforation or, sometimes fatal gastrointestinal bleeding, vomiting, flatulence, constipation, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis, Crohn's disease, gastritis.
Hepato-biliary disorders	Frequency unknown	Abnormal liver function tests.
Skin and subcutaneous tissue disorders	Frequent	Bullous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis.
	Frequency unknown	Hypersensitivity reactions - skin rashes and itching, exfoliative dermatitis.
Renal and urinary disorders	Frequency unknown	Impairment of renal function, acute reversible renal failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. A delay in starting treatment may mean that 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 microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

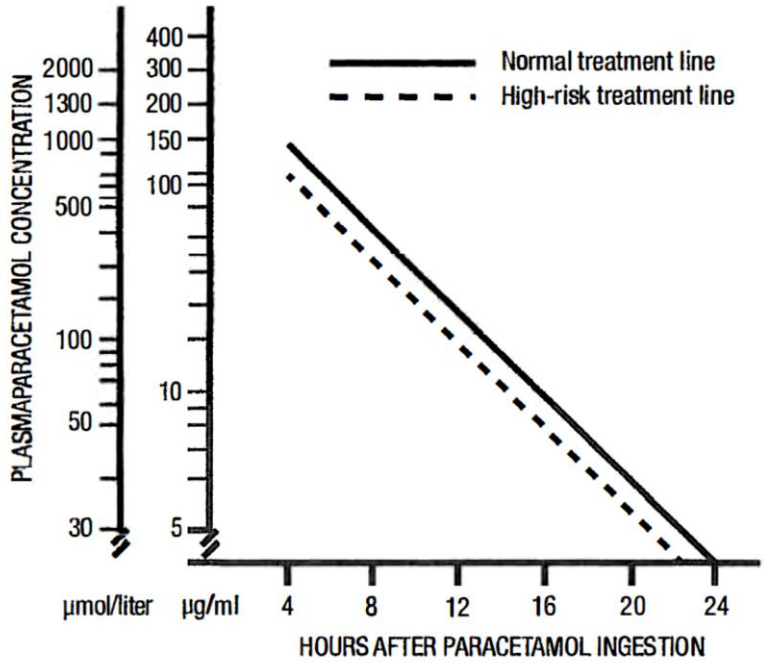
Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 48 hours, or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase 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.

Treatment for paracetamol overdosage

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration. N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, 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 an 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 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 overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour 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. Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV 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.



Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

2.8 Analgesic combinations

ATC code: N02BE51 - paracetamol, combinations excl. psycholeptics

Paracetamol

Paracetamol is an analgesic and antipyretic medicine. The precise mechanism has not yet been established.

Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic, and anti-inflammatory activities. Like other NSAIDs, ibuprofen is believed to work by inhibiting cyclooxygenase (COX), thus inhibiting prostaglandin synthesis.

Co-administration of ibuprofen and paracetamol

Combined use of paracetamol and an NSAID like ibuprofen is useful in the management of more severe pain, where combined use allows lower dosages of NSAIDS to be used, thereby minimizing overall side-effects.

5.2 Pharmacokinetic properties

Absorption

Both paracetamol and ibuprofen, are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

Paracetamol is rapidly and completely absorbed following oral administration, by passive diffusion throughout the gastrointestinal tract. In humans approximately 75 to 95 % of an oral dose is absorbed. Because of the high clearance of paracetamol resulting primarily from conjugation, the half-life is short, ranging from 2 to 3 hours.

Ibuprofen is rapidly absorbed with an absolute bioavailability approaching 100 %. The volume of distribution is small due to the physicochemical properties of the molecule and high protein binding to albumin. As a result of extensive oxidative metabolism and glucuronidation, the half-life is short, about 2 hours. The high protein binding is also concentration dependent, and as a result, total medicine exposures do not rise in proportion to the administered dose.

Repeat daily doses are necessary to maintain adequate plasma concentrations of paracetamol and ibuprofen.

Distribution

Paracetamol is not extensively bound to plasma proteins and independent of paracetamol concentration. Paracetamol is distributed into most body tissues. It readily crosses into the cerebrospinal fluid and into the brain, where it exhibits its main analgesic effect. Paracetamol readily crosses cell membranes and has a volume of distribution of about 0,9 L/kg in humans.

Ibuprofen is highly bound (90-99 %) to plasma proteins. In humans, more than 99 % of ibuprofen in serum is protein-bound; despite this, displacement interactions with other medicines are not clinically significant.

Biotransformation

Both paracetamol and ibuprofen are metabolised primarily by the liver. Paracetamol metabolites include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage. Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

Elimination

The elimination half-life of ibuprofen from plasma is in the range of 1,9 to 2,2 hours. The elimination half-life of paracetamol from plasma varies from about 1 to 3 hours. The main route of elimination from the body is in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 5 % of a paracetamol dose is excreted unchanged.

Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95 % of the administered dose eliminated in the urine within 4 hours of ingestion.

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Croscarmellose sodium

Magnesium stearate

Maize starch

Microcrystalline cellulose

Pregelatinised maize starch

Talc

Film-coating:

Opadry white OYLS 58900 (ID 3441):

HPMC 2910/Hypromellose 15 cP (E464)

Lactose monohydrate

Macrogol/PEG 4000

Sodium citrate dihydrate (Trisodium citrate) (E331)

Titanium dioxide (E171)

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC. Store in the original container to protect from light.

6.5 Nature and contents of container

Available in PVC/Alu blister packs containing 8, 10, 16, 20, 24, 30 tablets in an outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

8 REGISTRATION NUMBER

48/2.8/1263

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 18 May 2022

10 DATE OF REVISION OF THE TEXT

28 February 2025