PROPOSED CLEAN PACKAGE INSERT

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

MOLUMUS® 200 hard gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains Molnupiravir 200 mg.

Sugar Free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin Capsules.

MOLUMUS® 200 is a size '2' (i.e., Cap (mm) = 6.37 ± 0.03 and body (mm) = 6.08 ± 0.03) hard gelatin white opaque color capsules, filled with white to off white color granular powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MOLUMUS® 200 (molnupiravir) capsules are indicated for the treatment of mild and moderate coronavirus disease (Covid-19) in adults with a positive SARS-COV-2 diagnostic test who do not require supplemental oxygen due to Covid-19 and who have at least one risk factor for developing severe illness. [see section 5.1 Clinical Studies]

4.2. Posology and method of administration

Posology

Adults:

The recommended dose of MOLUMUS® 200 is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. Should a patient require hospitalization after starting treatment with MOLUMUS® 200, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

The safety and efficacy of MOLUMUS® 200 when administered for periods longer than 5 days have not been established.

MOLUMUS® 200 should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset in adults who are at risk for progression to severe COVID-19, including hospitalization or death. Certain medical conditions or other factors may place individual patients at increased risk for progression to severe COVID-19 (See section 5.1 Clinical Studies).

Missed dose:

If the patient misses a dose of MOLUMUS® 200 within 10 hours of the time it is usually taken, the patient should take as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Special populations

Elderly Population:

No dose adjustment of MOLUMUS® 200 is recommended for elderly patients based on age (See section 5.2 Gender, Race and Age).

Renal impairment:

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with renal eGFR less than 30 mL/min.

Hepatic impairment:

No dose adjustment of MOLUMUS® 200 is recommended in patients with hepatic impairment (See section 5.2 Hepatic Impairment).

Paediatric population

The safety and efficacy of MOLUMUS® 200 in patients below 18 years of age have not been established. No data are available (See section 5.2 Paediatric Population and 5.3 General Toxicity).

Pregnancy

Based on animal data, MOLUMUS® 200 may cause foetal harm. Human pregnancy data are not available. The use of MOLUMUS® 200 is not recommended during pregnancy [see section **5.3** Development].

Method of administration

For oral use.

MOLUMUS® 200 capsules can be taken with or without food.

The capsules should be swallowed whole with a sufficient amount of fluid (e.g., a glass of water). The capsules should not be opened, crushed, or chewed.

4.3. Contraindications

Hypersensitivity to the molnupiravir or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Sodium:

This medicinal product contains less than 1 mmol sodium per dose of four 200 mg capsules, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

No interactions have been identified based on the limited available data. No clinical interaction studies have been performed with Molnupiravir. Molnupiravir is hydrolysed to n-hydroxycytidine (NHC) prior to reaching systemic circulation. Uptake of NHC and metabolism to NHC-TP are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major medicine metabolising enzymes or transporters. Based on in vitro studies, neither Molnupiravir nor NHC are inhibitors or inducers of major medicine metabolising enzymes or inhibitors of major medicine transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Advise women of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of MOLUMUS® 200.

Pregnancy

Risk Summary

Based on animal data, MOLUMUS® 200 may cause foetal harm when administered to pregnant women. There are no available data on the use of MOLUMUS® 200 in pregnant women to evaluate the risk of major birth defects, miscarriage or adverse maternal or foetal outcomes. The use of MOLUMUS® 200 is not recommended during pregnancy. In an animal reproduction study, oral administration of molnupiravir to pregnant rats

during the period of organogenesis resulted in embryofoetal lethality and teratogenicity at 8 times the human NHC exposures at the recommended human dose (RHD) and reduced foetal growth at ≥ 3 times the human NHC exposure at the RHD.

Oral administration of molnupiravir to rabbits during the period of

organogenesis resulted in reduced foetal body weights at 18 times the human NHC exposure at the RHD [see section **5.3** Development]. In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up

to 500 mg/kg/day (1.6 times the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

Breast-feeding

It is unknown whether MOLUMUS® 200 or any of the components of MOLUMUS® 200 are present in human milk, affect human milk production, or have effect on the breastfed infant. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir. Based on the potential for adverse reactions on the infant from MOLUMUS® 200, breast-feeding is not recommended during treatment and for 4 days after the last dose of MOLUMUS® 200.

Fertility

There were no effects on female or male fertility in rats at NHC exposures approximately 2 and 6 times respectively, the exposure in humans at the recommended human dose (RHD) (See section 5.3).

4.7. Effects on ability to drive and use machines

MOLUMUS® 200 has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of safety profile:

The most common adverse reactions in patients treated with 800 mg molnupiravir every 12 hours for 5 days in the Phase 3 MOVe-OUT clinical trial were diarrhoea (2%), nausea (1%), dizziness (1%) all of which were Grade 1 (mild) or Grade 2 (moderate) in severity.

Tabulated list of adverse reactions:

Table 1: Tabulated list of adverse reactions

Frequency	**Adverse Reaction**
Immune System Disorders	
Less Frequent	hypersensitivity
Nervous system disorders:	
Frequent	dizziness, headache
Gastrointestinal disorders:	
Frequent	diarrhoea, nausea
Less Frequent	vomiting
Skin and subcutaneous tissue disorders:	
Less Frequent	angioedema, erythema, rash, urticaria

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

There is no human experience of overdosage with MOLUMUS® 200. Treatment of overdose with MOLUMUS® 200 should consist of general supportive measures including the monitoring of the clinical status of the patient. Haemodialysis is not expected to result in effective elimination of NHC.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals.

A20.2.8 Antiviral agents

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

Mechanism of action:

MOLUMUS® 200 is a prodrug that is metabolised to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHCTP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

Microbiology

Antiviral Activity:

NHC was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC50) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells.

NHC had similar activity against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with EC50 values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively. No impact was observed on the in vitro antiviral activity of NHC against SARSCoV-2 when NHC was tested in combination with abacavir, emtricitabine, hydroxychloroquine, lamivudine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir.

Resistance:

No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19.

Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance associated amino acid substitutions were identified. NHC retained activity *in vitro* against virus with polymerase substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

Activity against SARS-CoV-2 in animal models

The antiviral activity of molnupiravir has been demonstrated in mouse, hamster and ferret models of SARS-CoV-2 infection. In mice, molnupiravir significantly reduced infectious SARS-CoV-2 levels in infected transplanted human lung tissue. In SARSCoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection, showed significantly reduced SARS-CoV-2 viral

antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

Clinical efficacy and safety:

Clinical data are based on data from 1,433 randomised subjects in the Phase 3 MOVe-OUT trial.MOVe-OUT was a randomised, placebo-controlled, double-blind clinical trial studying Molnupiravir for the treatment of non-hospitalised patients with mild to moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalisation.

Eligible subjects were 18 years of age and older and had one or more predefined risk factors for disease progression: over 60 years of age or older, diabetes, obesity (BMI >30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of enrolment. Subjects were randomised 1:1 to receive 800 mg of MOLUMUS 200 or placebo orally twice daily for 5 days.

At baseline, in all randomised subjects, the median age was 43 years (range: 18 to 90 years); 17% of subjects were 60 years of age and 3% were over 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian; 50% were Hispanic or Latino. Forty-eight percent of subjects received molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), 60 years of age (17%), and diabetes (16%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Table 2 provides the results of the primary endpoint (the percentage of subjects who were hospitalised or died through day 29 due to any cause). Please refer to Figure 1 for results by certain subgroups.

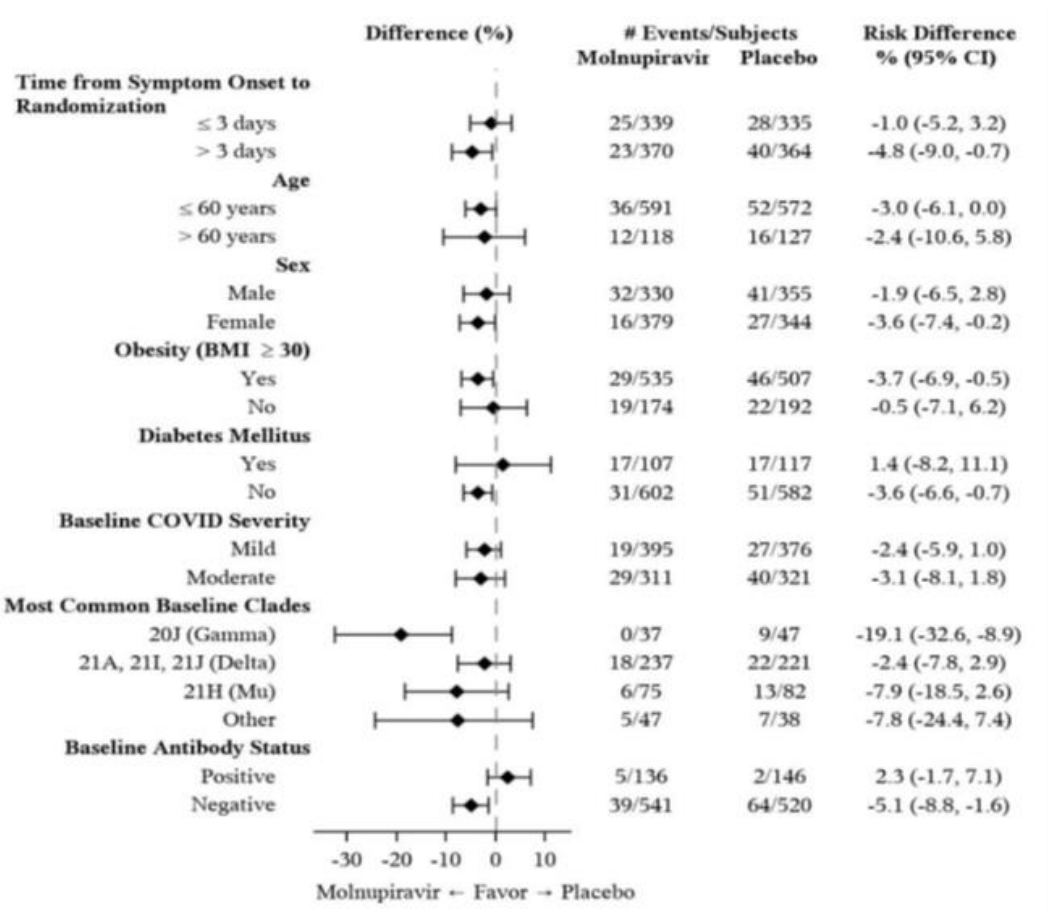
Table 2: Interim Efficacy Results in Non-Hospitalised Adults with COVID-19

Molnupiravir (N=709) n (%)	**Placebo (N=699) n (%)**	***Adjusted Risk difference* (95% CI)***
All-cause hospitalisation or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0,1%)	9 (1,3%)	

*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024. Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%). Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

Efficacy results were consistent across sub-groups including age (>60 years), at risk medical conditions (e.g., obesity, diabetes) baseline Covid-19 severity (mild, moderate) and SARS-CoV-2 variants.

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method. The modified intent-to-treat population is the efficacy analysis population. Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein. The findings of these subgroup analyses are considered exploratory.

Higher percentages of subjects reported sustained improvement or resolution in most self-reported COVID-19 signs and symptoms, as recorded on a daily symptom diary, in the LAGEVRIOTM group compared to the placebo group.

5.2. Pharmacokinetic properties

Molnupiravir is a 5´-isobutyrate prodrug that is hydrolysed to NHC prior to reaching systemic circulation. The pharmacokinetics of NHC are similar in healthy subjects and patients with COVID-19.

The pharmacokinetics of NHC at steady state following administration of 800 mg Molnupiravir every 12 hours are provided below in Table 3.

Table 3: Pharmacokinetics of NHC after administration of 800 mg Molnupiravir every 12 hours

NHC Geometric Mean (%CV)		
AUC0-12hr (ng×hr/mL)*	C_{max} (ng/mL) †	C12hr (ng/mL)*
8260 (41.0)	2970 (16.8)	31.1 (124)
%CV: Geometric coefficient of variation. * Values were obtained from population PK analysis. †Values were obtained from a Phase 1 study of healthy subjects.		

Absorption:

Following twice daily oral administration of 800 mg Molnupiravir, the median time to peak plasma NHC concentrations (T_{max}) was 1.5 hours.

Effect of Food on Oral Absorption

In healthy subjects, the administration of a single 200 mg dose of MOLUMUS® 200 with a high-fat meal resulted in a 35% reduction in NHC peak concentrations (C_{max}), AUC was not significantly affected.

Distribution:

NHC does not bind to plasma proteins.

Elimination:

The effective half-life of NHC is approximately 3.3 hours. The fraction of dose excreted as NHC in the urine was ≤3% in healthy participants.

Other special populations

Gender, Race, Age:

Population pharmacokinetic analysis showed that age, gender, race and ethnicity do not meaningfully influence the pharmacokinetics of NHC.

Paediatric Patients:

The pharmacokinetics of molnupiravir in paediatric patients less than 18 years of age have not been evaluated.

Renal Impairment:

Renal clearance is not a meaningful route of elimination for NHC. No dose adjustment in patients with any degree of renal impairment is needed. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics of NHC.

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure [see section **4.2** Renal Impairment].

Hepatic Impairment:

The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with moderate or severe hepatic impairment. In a population pharmacokinetic analysis, the AUC_{0-12} of NHC was 5 % higher in subjects with mild hepatic impairment, compared to healthy subjects. This difference is not considered clinically relevant. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination. No dose adjustment in patients with hepatic impairment is needed (See section 4.2).

5.3. Preclinical safety data

General Toxicity:

Reversible, dose-related bone marrow toxicity affecting all haematopoietic cell lines was observed in dogs at ≥17mg/kg/day (0.4 times the human NHC exposure at the recommended human dose (RHD)). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of Molnupiravir treatment progressing to more severe haematological changes after 14 days of treatment. Neither bone marrow nor haematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9.3 and 15 times the human NHC exposure at the RHD in females and males, respectively).

Bone and cartilage toxicity, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone was observed in the femur and tibia of rapidly growing rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5.4 times the human NHC exposure at the RHD).

There was no bone or cartilage toxicity in a 1-month toxicity study in rapidly growing rats up to 500 mg/kg/day (4.2 and 7.8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (1.6 times the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD). Growth cartilage is not present in mature skeletons; therefore, the bone and cartilage findings are not relevant for adult humans.

The clinical significance of these findings for Paediatric patients is unknown.

Carcinogenesis:

Carcinogenicity studies with molnupiravir have not been conducted.

Mutagenesis:

Molnupiravir and NHC were positive in the in vitro bacterial reverse mutation assay (Ames assay) with and without metabolic activation. In 2 distinct in vivo rodent mutagenicity models (Pig-a mutagenicity assay and Big Blue® (cII Locus) transgenic rodent assay) molnupiravir did not induce increased mutation rates relative to untreated historical control animals, and therefore is not mutagenic in vivo. Molnupiravir was negative for induction of chromosomal damage in in vitro micronucleus (with and without metabolic activation) and in vivo rat micronucleus assays. Based on the totality of the genotoxicity data, molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use.

Reproduction:

There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the recommended human dose (RHD).

Development:

In an embryofoetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250 or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased foetal body weights and delayed ossification at ≥500 mg/kg/day (2.9 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (0.8 times the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of individual animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced foetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD).

Maternal toxicities included reduced food consumption and body weight gains, and abnormal faecal output at 750 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients.

Capsule content:

- Crospovidone (Polyplasdone XL-10).
- Colloidal Silicon Dioxide (Aerosil 200).
- Microcrystalline Cellulose[2] (XLM90).
- Povidone K-30 (Kollidon 30).
- Sodium Stearyl Fumarate (PRUV)

Capsule shells content:

- Gelatin.
- Opacifier (i.e., Titanium Dioxide).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 Months.

6.4. Special precautions for storage

There are no special storage instructions for MOLUMUS®200.

Store in the original package below 25°C.

Do not use after the expiry date stated on the label / carton.

Keep the container in the outer carton. Keep out of reach of children.

6.5. Nature and contents of container

MOLUMUS® 200 is size '2' (i.e., Cap (mm) = 6.37 ± 0.03 and body (mm) = 6.08 ± 0.03) hard gelatin white opaque colour capsules, filled with white to off white colour granular powder.

PVC/PVDC Alu pack of 10 Capsules.

6.6. Special precautions for disposal and other handling

Keep out of reach of Children.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

BLISS PHARMACEUTICALS (PTY) LTD

107 Northern Parkway,

Unit 6, Ormonde Business Park,

Ormonde 2091,

Johannesburg, RSA.

8. REGISTRATION NUMBER

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT

To be allocated