PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CAGOL 600/ 50/300 mg film-coated tablets

HYPERSENSITIVITY REACTIONS

Hypersensitivity to abacavir (see also section 4.8).

In clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction, which in some cases has proved fatal.

Risk Factors:

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % (66 of 847) to 3,4 % (27 of 803) ($p < 0,0001$) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % (23 of 842) to 0,0 % (0 of 802) ($p < 0,0001$). Based on this study, it is estimated that 48 % to 61 % of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-B*5701 allele.

Clinicians should screen for carriage of the HLA-B*5701 allele in any HIV infected patient without prior exposure to abacavir. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-

B*5701 status who have previously tolerated abacavir. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.
In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Clinical Description:

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome.
Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised). The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical Management:

Regardless of their HLA-B*5701 status, any patient developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed CAGOL MUST be discontinued immediately. CAGOL, or any other medicinal product containing abacavir, MUST NEVER be restarted following a hypersensitivity reaction, as more severe symptoms will

recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, **CAGOL** should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medicines). **CAGOL**, or any other medicinal product containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medicine(s).

An Alert Card with information for the patient about this hypersensitivity reaction is included in the **CAGOL** pack.

Special considerations following an interruption of CAGOL therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with any abacavir containing product has been discontinued and restarting therapy with **CAGOL** is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, CAGOL or any other medicinal product containing abacavir should not be restarted.**

There have been infrequent reports of hypersensitivity reaction following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart **CAGOL** in these patients, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart **CAGOL**, this

must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA-B*5701 allele is not recommended.

Essential patient information:

Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.
- Patients must also be informed that HLA-B*5701 negative patients can also experience abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir **MUST CONTACT** their doctor **IMMEDIATELY.**
- Patients who are hypersensitive to abacavir should be reminded that they must never take **CAGOL** or any other medicinal product containing abacavir again, regardless of their HLA-B*5701 status.
- In order to avoid restarting **CAGOL**, patients who have experienced a hypersensitivity reaction should be asked to return the remaining **CAGOL** tablets to the pharmacy.
- Patients who have stopped **CAGOL** for any reason and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each patient should be reminded to read the package leaflet included in the **CAGOL** pack. They should be reminded of the

importance of removing the Alert Card included in the pack and keeping it with them at all times.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

600 mg of abacavir as abacavir sulphate, 50 mg of dolutegravir as dolutegravir sodium and 300 mg of lamivudine

Excipient(s) with known effect:

Contains sugar: Mannitol (184,38 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Light blue to blue, oval shaped, film-coated tablets debossed with "EM" on one side and "35" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CAGOL is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents from 18 years of age, who are antiretroviral treatment-naive or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral medicines in **CAGOL**.

4.2 Posology and method of administration

Posology

CAGOL therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults and adolescents (weighing at least 40kg):

The recommended dose of **CAGOL** in adults and adolescents is one tablet once daily.

CAGOL is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of dolutegravir, abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases, the medical practitioner should refer to the individual product information for these medicines. Since the recommended dosage of dolutegravir is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of **CAGOL** is not recommended for patients with integrase inhibitor resistance.

Elderly:

There are limited data available on the use of dolutegravir, abacavir and lamivudine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2 – Special Patient Populations). Special care is advised in this age group due to age associated changes such as the decrease in hepatic, renal and cardiac function, concomitant medicines or disease.

Renal impairment:

Whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore, **CAGOL** is not recommended for use in patients with a creatinine clearance < 50 ml/min (see section 5.2– Special Patient Populations and section 4.3).

Hepatic impairment:

A dose reduction of abacavir may be required for patients with mild hepatic impairment (Child-Pugh grade A). As dose reduction is not possible with **CAGOL,** the separate preparations of dolutegravir, abacavir or lamivudine should be used when this is judged necessary. **CAGOL** is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see section 5.2– Special Patient Populations and section 4.3).

Paediatric population

CAGOL should not be administered to patients younger than 18 years old.

Method of administration

CAGOL can be taken with or without food.

4.3 Contraindications

CAGOL is contraindicated in patients with known hypersensitivity to dolutegravir, abacavir or lamivudine or to any of the components of the product.

CAGOL is contraindicated in combination with dofetilide and pilsicainide.

CAGOL is contraindicated in moderate and severe hepatic impairment due to the abacavir component (see section 5.2).

Metformin is contraindicated in patients taking **CAGOL.**

CAGOL is contraindicated in pregnancy and lactation.

CAGOL is contraindicated in patients with renal impairment with a creatinine clearance < 50 ml/min.

4.4 Special warnings and precautions for use

Warnings relevant to dolutegravir, abacavir and lamivudine are included in this section. There are no additional warnings relevant to **CAGOL**.

Hypersensitivity: Abacavir (refer to boxed warning at the beginning of this Professional Information and under section 4.8)

Hypersensitivity: Dolutegravir

Discontinue **CAGOL** immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferase should be monitored and appropriate therapy initiated. Delay in stopping treatment with **CAGOL** or other suspect medicines after the onset of hypersensitivity may result in a life- threatening reaction.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate

treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving **CAGOL** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **CAGOL**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo*

to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/ hyperlactataemia (see below), other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/ children, should have clinical and laboratory follow up and should be investigated for possible mitochondrial damage.

Pancreatitis

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **CAGOL** until diagnosis of pancreatitis is excluded.

Lactic acidosis/ severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of abacavir and lamivudine. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude

other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.

- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Diagnosis of lactic acid is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any patient with a raised lactate level. Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided. Seek expert advice on medicine selection. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **CAGOL** alone or in combination. Caution should be exercised when administering **CAGOL** to any patient, and particularly to those with known risk factors for liver disease. Treatment with **CAGOL** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Cardiovascular events

Although the available data from clinical and clinical observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir.

Therefore, when prescribing **CAGOL**, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

In addition, alternative treatment options to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

Medicine interactions

Caution should be given to co-administering medicines (prescription and non-prescription) that may change the exposure of **CAGOL** or medicines that may have

their exposure changed by **CAGOL** (see section 4.3 and section 4.5). The co-administration of **CAGOL** with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV) (see section 4.5).
Dolutegravir should not be co-administered with polyvent cation- containing antacids. Dolutegravir is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5).
CAGOL is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (see section 4.5).
Metformin concentrations may be increased by **CAGOL**.
Metformin is contra-indicated in patients taking **CAGOL** (see section 4.3).
CAGOL should not be administered concurrently with other medicinal products containing any of the same active components (dolutegravir, abacavir and/ lamivudine).
Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking efavirenz, nevirapine, rifampicin and tipranavir/ritonavir, the use of **CAGOL** is not recommended for patients taking these medicines (see section 4.5).

Co-infection with Hepatitis B or C virus (HBV)
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.
Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy when starting therapy with **CAGOL** in hepatitis B co-infected patients.

Clinical study and marketed use of lamivudine, have shown that some patients with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If **CAGOL** is discontinued in patients co-infected with HBV, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

4.5 Interactions with other medicines and other forms of interaction

TABLE 1: Medicine Interaction study reports with dolutegravir

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of CAGOL or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC↓71 % C_{max}↓52 % C_{τ} ↓ 88 % ETR ↔	Etravirine decreased dolutegravir plasma concentration, which may result in loss of virologic response and possible resistance to dolutegravir. **CAGOL** should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC↓57 % C_{max}↓39 % C_{τ} ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor:	Dolutegravir ↑	Atazanavir increased

Atazanavir (ATV)	AUC↑91 % C_{max}↑49 % C_{τ} ↑ 180 % ATV ↔	dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC↑62 % C_{max}↑33 % C_{τ} ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC↓59 % C_{max}↓47 % C_{τ} ↓ 76 % TPV ↔ RTV↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ AUC↓35 % C_{max}↓24 % C_{τ} ↓ 49 % FPV ↔ RTV↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ C_{τ}↔ LPV↔ RTV↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV + RTV)	Dolutegravir ↓ AUC↓32 % C_{max}↓11 % C_{τ} ↓ 38 % DRV ↔ RTV↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)0	Dolutegravir ↔ TDV↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC↑10 % C_{max}↑7 % C_{τ} ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↔ AUC↓25 % C_{max}↓12 % C_{τ} ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Medicines		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC↓74 % C_{max}↓72 % C_{24}↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. **CAGOL** is recommended to be administered 2 hours before or 6 hours after taking antacid medicines containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC↓39 % C_{max}↓37 % C_{24}↓ 39 %	**CAGOL** is recommended to be administered 2 hours before or 6 hours after taking medicines containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC↓549 % C_{max}↓57 % C_{24}↓ 56 %	**CAGOL** is recommended to be administered 2 hours before or 6 hours after taking medicines containing iron, or alternatively, administer with food.
Metformin	Metformin↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contra-indicated in patients taking **CAGOL** (see section 4.3).
Rifampicin	Dolutegravir ↓ AUC↓54 % C_{max}↓43 % C_{τ}↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily

		when co-administered with rifampicin. The co-administration is not recommended.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN)	Effect of dolutegravir: EE↔ AUC↑ 3 % C_{max}↓1 % C_{τ} ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11% C_{τ}↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max}↔ 0 % C_{τ} ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with dolutegravir.

Abbreviations:

↑ = increase

↓ = decrease

↔ = no significant change

AUC = area under the concentration versus time curve

C_{max} = maximum observed concentration

C_{τ} = concentration at the end of dosing interval

Table 2 Medicine interactions study reports with abacavir

Concomitant medicine class: Medicine name	**Effect on concentration of abacavir or concomitant medicine**	**Clinical comment**
Methadone (40 to 90 mg once daily for 14 days/600 mg single dose, then 600 mg twice daily for 14 days)	Abacavir AUC ↔ C_{max} ↓ 35 % Methadone CL/F ↑ 22 %	The changes in abacavir pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics are not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.
Ethanol	Abacavir AUC ↑ 41 % Ethanol AUC ↔	Given the safety profile of abacavir, these findings are not considered clinically significant.

Abbreviations:

↑ = increase

↓ = decrease

↔ = no significant change

AUC = area under the concentration versus time curve

C_{max} = maximum observed concentration

CL/F =apparent clearance

Table 3 Medicine interactions study reports with lamivudine

Concomitant medicine class: Medicine name	**Effect on concentration of lamivudine or concomitant medicine**	**Clinical comment**
Trimethoprim/sulfamethoxazole (co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of Pneumocystis jirovecl (P. carinil) pneumonia and toxoplasmosis has not been studied. **CAGOL** should not be used for subjects with CLcr of < 50 ml/min (see section 4.3).
Emtricitabine		Lamivudine may inhibit the intracellular phosphorylation of emtriciabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **CAGOL** is therefore not recommended to be used in combination with zalcitabine.

Zidovudine		Although there is usually no clinically significant interaction with zidovudine, severe anaemia has occasionally been reported in patients given lamivudine with zidovudine.

4.6 Fertility, pregnancy and lactation

***Women of childbearing potential / Contraception in males and females*:**

Women of childbearing potential (WOCBP) should be counselled about the potential risk of neural tube defects with dolutegravir (a component of **CAGOL**, see below), including consideration of effective contraceptive measures.

If a woman plans pregnancy, the benefits and the risks of continuing treatment with **CAGOL** should be discussed with the patient.

Pregnancy:

Safety during pregnancy in humans have not been established. **CAGOL** should not be used during pregnancy as teratogenicity has been observed in animal studies (see section 4.3). Dolutegravir, lamivudine and abacavir were shown to cross the placenta in reproductive toxicity studies in animals. There have been reports of elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir and lamivudine. The clinical relevance of transient elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease.

Breastfeeding:

Safety during lactation in human use have not been established. **CAGOL** should not be used during lactation as teratogenicity has been observed in animals (see section 4.3). HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. It is expected that abacavir and dolutegravir will be secreted into human milk. Lamivudine is excreted in human milk at similar concentrations to those found in serum. Therefore, mothers breastfeeding their infants should not use **CAGOL.**

Fertility

There are no data on the effects of dolutegravir, abacavir or lamivudine on human male or female fertility. Animal studies indicate no effects of dolutegravir, abacavir or lamivudine on male or female fertility.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of **CAGOL** on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of CAGOL should be borne in mind when considering the patients' ability to drive or operate machinery. Patients should be informed that dizziness has been reported during treatment with dolutegravir.

4.8 Undesirable effects

Abacavir hypersensitivity (also refer to boxed warning at the beginning of this Professional Information)

In clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction (HSR), which in some cases have proved fatal. This reaction is characterized by the appearance of symptoms indicating multi-organ/ body-system involvement. Almost all patients developing hypersensitivity reactions will have fever and/ or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever. Symptoms can occur at any time during treatment, but usually appear within the first six weeks (median time to onset 11 days). The signs and symptoms of this hypersensitivity reaction are listed below. Those reported in at least 10% of patients with a hypersensitivity reaction is in **bold text.**

Skin and subcutaneous tissue disorders:

Rash (usually maculopapular or urticarial)

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration

Respiratory, throat and mediastinal disorders:

Dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure

General disorders and administration site conditions:

Fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Nervous system disorders:

Headache, paraesthesia

Blood and lymphatic system disorders:

Lymphopenia

Hepato-biliary disorders:

Elevated liver function tests, hepatic failure

Musculoskeletal connective tissue and bone disorders:

Myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase

Renal and urinary disorders:

Elevated creatinine, renal failure

Some patients with hypersensitivity were initially thought to have respiratory disease, a flu-like illness, gastroenteritis or reactions to other medicines. This delay in diagnosis resulted in abacavir being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. The diagnosis of hypersensitivity reaction should therefore be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity cannot be ruled out, **CAGOL** or any medicine containing abacavir should not be restarted. Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is

usually more severe than on initial presentation and may include life-threatening hypotension and death. Similar reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

Tabulated summary of adverse reactions

Table 4: Side-effects which have been associated with the individual components of CAGOL and combination of dolutegravir + abacavir/lamivudine:

	Dolutegravir	**Abacavir**	**Lamivudine**	**Combination of dolutegravir + abacavir/lamivudine**
Blood and lymphatic system disorders:				
Less frequent:			neutropenia, anaemia, thrombocytopenia	Neutropenia[1], anaemia[1], thrombocytopenia[1] pure red cell aplasia[1]
Immune system disorders:				
Frequent:		medicine hypersensitivity		hypersensitivity (see section 4.4)
Less frequent:	hypersensitivity, immune reconstitution syndrome			immune reconstitution syndrome (see section 4.4)
Metabolism and nutrition disorders:				
Frequent:		anorexia		anorexia[1]
Less frequent:				hypertriglyceridaemia, hyperglycaemia, lactic acidosis[1]
Psychiatric disorders:				
Frequent:	insomnia, abnormal dreams			insomnia, abnormal dreams, depression, anxiety[1], nightmare, sleep disorder
Less frequent:				suicidal ideation or suicide attempt (particularly in patients with a pre-

				existing history of depression or psychiatric illness)
Nervous system disorders:				
Frequent:	headache, dizziness	headache	headache	headache, dizziness, somnolence, lethargy[1]
Less frequent:				peripheral neuropathy[1], paraesthesia[1]
Respiratory, thoracic and mediastinal disorders:				
Frequent:				cough[1], nasal symptoms[1]
Gastrointestinal disorders:				
Frequent:	nausea, diarrhoea, vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort	nausea, diarrhoea, vomiting,	nausea, diarrhoea, vomiting, upper abdominal pain	nausea, diarrhoea, vomiting, flatulence, abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, gastro-oesophageal reflux disease, dyspepsia
Less frequent:				pancreatitis[1]
Hepatobiliary disorders:				
Less frequent:	hepatitis		transient rises in liver enzymes (AST, ALT)	hepatitis, acute hepatic failure[1]
Skin and subcutaneous tissue disorders:				
Frequent:	rash, pruritus		rash	rash, pruritus, alopecia[1]
Less frequent:				erythema multiform[1], Stevens-Johnson syndrome[1], toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders:				
Frequent:				Arthralgia[1], muscle disorders[1](including myalgia[1])
Less frequent:				rhabdomyolysis[1]
General disorders and administration site conditions:				
Frequent:	fatigue	fever, lethargy, fatigue	fatigue, malaise, fever	fatigue, asthenia, fever[1], malaise[1]
Investigations:				
Frequent:				CPK elevations, ALT/AST elevations
Less frequent:				amylase elevations[1]

[1]This adverse reaction was identified from clinical studies or post-marketing experience for dolutegravir, abacavir or lamivudine when used with other antiretrovirals or post-marketing experience with **CAGOL.**

Description of selected adverse reactions

Changes in laboratory chemistries*:*

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. A mean change from baseline of 12,6 µmol/l was observed after 96 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

Post-marketing data:

In addition to the side effects included from clinical trial data, the side effects listed in Table 5 below have been identified during post-approval use of abacavir and lamivudine. No dolutegravir or **CAGOL** post-marketing data are available.

Table 5: Side effects based on post-marketing experience

System organ class	**Abacavir**	**Lamivudine**
Blood and lymphatic systems disorders		pure red cell aplasia
Metabolism and nutrition disorders	hyperlactataemia [1]lactic acidosis	hyperlactataemia [1]lactic acidosis

Nervous system disorders		paraesthesiae, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain
Gastrointestinal disorders	pancreatitis, but a causal relationship to abacavir is uncertain	rises in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain
Skin and subcutaneous tissue disorders	rash (without systemic symptoms) erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	alopecia
Musculoskeletal and connective tissue disorders		arthralgia, muscle disorders rhabdomyolysis

[1]Lactic acidosis (see section 4.4).

Redistribution/accumulation of body fat has been observed in some patients receiving combination antiretroviral therapy (see section 4.4),

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 Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with dolutegravir, abacavir or lamivudine, apart from those listed as side effects. There is no specific treatment for an overdose of **CAGOL.** If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR13

Mechanism of action:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values 2,7 nM and 12,6 nM *in vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{1/2}$ 71 hours).

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) and are selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties with extended intracellular half-lives supporting once daily dosing. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the

monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

5.2 Pharmacokinetic properties

The **CAGOL** tablet has been shown to be bioequivalent to dolutegravir single entity tablet with abacavir/lamivudine fixed dose combination tablet administered separately. There was no clinically significant effect of a high fat meat on the exposure of abacavir or lamivudine with dolutegravir; a high fat meal increased the C_{max} by 37 % and the AUC by 48 %. These results indicate that **CAGOL** can be taken with or without food.

The pharmacokinetic properties of dolutegravir, lamivudine and abacavir are described below.

Absorption:

Dolutegravir, abacavir and lamivudine are absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral abacavir and lamivudine in adults is 83 % and 80 to 85 % respectively. The mean time to maximal serum concentrations (T_{max}) is about 2 to 3 hours (post dose for tablet formulation) for dolutegravir, 1,5 hours for abacavir and 1,0 hours for lamivudine. Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 53,6 µg.h/ml for AUC_{24}, 3,67 µg/ml for C_{max}, and 1,11 µg/ml for C_{24}. Following a single oral dose of 600 mg of abacavir, the mean C_{max} is 4,26 µg/ml and the mean AUC_{∞} is 11,95 µg.h/ml. Following multiple- dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2,04 µg/ml and the mean AUC_{24} is 8,87 µg.h/ml.

Distribution:

The apparent volume of distribution of dolutegravir is estimated at 12,5 l. Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins

based on *in vitro* data. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma medicine-related radioactivity with blood cellular components. Dolutegravir, abacavir and lamivudine are present in cerebrospinal fluid (CSF), CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 2,04 %. Study reports with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12%.

Biotransformation:

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by either glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose). Abacavir is primarily metabolised by the liver with less than 2 % of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the administered dose. These metabolites are excreted in the urine. Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 10 %).

Elimination:

Dolutegravir has a terminal half-life of ~ 14 hours and an apparent clearance (CL/F)

of 0,56 l/hr. The mean half-life of abacavir is about 1,5 hours. The geometric mean terminal half-life of intracellular carbovir-TP at steady-state is 20,6 hours. Following multiple oral doses of abacavir 300 mg twice a day, there is no significant accumulation of abacavir. Elimination of abacavir is *via* hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83 % of the administered abacavir dose in the urine. The remainder is eliminated in the faeces. The reported lamivudine half-life of elimination is 5 to 7 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0,32 l/h/kg, predominately by renal clearance (greater than 70 %) via the organic cationic transport system.

Special patient populations:

Elderly:

Pharmacokinetic data for dolutegravir, abacavir and lamivudine in subjects of > 65 years old are limited.

Renally impaired:

Pharmacokinetic data have been obtained for dolutegravir, abacavir and lamivudine alone. **CAGOL** should not be used in patients with creatinine clearance of less than 50 ml/min because, whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component. Therefore, the separate preparation of lamivudine should be used to treat these patients.

Study reports with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance.

Abacavir is primarily metabolized by the liver, with approximately 2 % of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Renal clearance of unchanged medicine is a minor pathway of elimination for

dolutegravir. A study report of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr < 30 ml/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 ml/min) and matching healthy subjects were reported. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatically impaired:

Pharmacokinetic data has been obtained for dolutegravir, abacavir and lamivudine alone. Based on data obtained for abacavir, **CAGOL** is not recommended in patients with moderate and severe hepatic impairment.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been reported in patients with hepatic impairment (Child-Pugh score 5 to 6). The results showed that there was a mean increase of 1,89-fold in the abacavir AUC and 1,58-fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. Dosage reduction of abacavir may be required in patients with mild hepatic impairment. The separate preparation of abacavir should therefore be used to treat these patients. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. **CAGOL** is therefore, not recommended in patients with moderate and severe hepatic impairment. Data obtained for lamivudine in patients with moderate to severe hepatic impairment and for dolutegravir in patients with moderate hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction. Dolutegravir is primarily metabolized and eliminated by the liver.

Polymorphisms in medicine metabolising enzymes:

There is no evidence that common polymorphisms in medicine metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent.

Co-infection with Hepatitis B or C:

Population PK analysis indicated that hepatitis C virus co-infection had no clinically

relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on subjects with hepatitis B co-infection.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Magnesium stearate, mannitol, microcrystalline cellulose, povidone and sodium starch glycolate

Tablet coating:

Contains FD&C blue #2/ Indigo carmine aluminum lake, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide (CI 778910]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

28's: 28 tablets are packed in a 75 ml, white opaque, wide mouth round HDPE (High Density Polyethylene) high wall container. The HDPE container is closed with a 38 mm, white opaque, continuous thread (screw), polypropylene closure with HS130-20 liner. A HDPE canister containing 1 g activated silica gel, with a printed

label, free from dust and visual defects is included in each container.

30's: 30 tablets are packed in a 75 ml, white opaque, wide mouth round HDPE (High Density Polyethylene) high wall container. The HDPE container is closed with a 38 mm, white opaque, continuous thread (screw), polypropylene closure with HS130-20 liner. A HDPE canister containing 1 g activated silica gel, with a printed label, free from dust and visual defects is included in each container. The container is packed in an outer carton along with a leaflet.

90's: 90 tablets are packed in a 200 ml, white opaque, wide mouth round HDPE (High Density Polyethylene) high wall container. The HDPE container is closed with a 38 mm, white opaque, continuous thread (screw), polypropylene closure with HS130-20 liner. A HDPE canister containing 2 g activated silica gel, with a printed label, free from dust and visual defects is included in each container. The container is packed in an outer carton along with a leaflet.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Emcure Pharmaceuticals SA (Pty) Ltd.
Arizona House, First floor, South Wing, Aspen Business Park
1 Madison Avenue, Aspen Lakes, Extension 13
Johannesburg South,
2190

8. REGISTRATION NUMBER(S)

54/20.2.8/0206

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 October 2020

10. DATE OF REVISION OF THE TEXT

7 June 2024