TABLE OF CONTENTS – CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION FEBRUARY 2022

CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION FEBRUARY 2022 3

SCHEDULING STATUS 3

1. NAME OF THE MEDICINE 3

2. QUALITATIVE AND QUANTITATIVE COMPOSITION 7

3. PHARMACEUTICAL FORM 7

4. CLINICAL PARTICULARS 7

4.1 Therapeutic indications 7

4.2 Posology and method of administration 7

4.3 Contraindications 9

4.4 Special warnings and precautions for use 9

4.5 Interaction with other medicines and other forms of interaction 14

4.6 Fertility, pregnancy and lactation 19

4.7 Effects on ability to drive and use machines 20

4.8 Undesirable effects 20

5. PHARMACOLOGICAL PROPERTIES 24

5.1 Pharmacodynamic properties 24

5.2 Pharmacokinetic properties 25

5.3 Preclinical safety data 28

6. PHARMACEUTICAL PARTICULARS 28

6.1 List of excipients 28

6.2 Incompatibilities 29

6.3 Shelf life 29

6.4 Special precautions for storage 29

6.5 Nature and contents of container 29

6.6 Special precautions for disposal and other handling 30

7. HOLDER OF CERTIFICATE OF REGISTRATION 30

8. REGISTRATION NUMBER(S) 30

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 30

VR

10.DATE OF REVISION OF THE TEXT.....30

VR

CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

QULAM-CO (film-coated tablets)

Hypersensitivity to abacavir (see also section **4.8**)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening and may be fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

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. In some cases, this 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

VR

abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-B*5701 allele.

It is recommended that any HIV-infected patient without prior exposure to abacavir be screened for HLA-B*5701 allele. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see *Special considerations following an interruption of* ***QULAM-CO*** *therapy*). 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 patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity

VR

reaction is diagnosed, QULAM-CO MUST be discontinued immediately. QULAM-CO, or any other medicine 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, **QULAM-CO** 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). **QULAM-CO**, or any other medicine 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 **QULAM-CO** pack.

Special considerations following an interruption of QULAM-CO therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with **QULAM-CO** or any abacavir containing medicine has been discontinued and restarting therapy with **QULAM-CO** 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, QULAM-CO or any other medicine 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 **QULAM-CO** in these patients, this should be done only under direct medical supervision.

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 **QULAM-CO**, this must be done only if medical care can be accessed readily by the patient or

VR

others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of **QULAM-CO** in patients of unknown HLA-B*5701 status who have previously tolerated **QULAM-CO**. Re-initiation of **QULAM-CO** 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 **QULAM-CO** or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.
- in order to avoid restarting **QULAM-CO**, patients who have experienced a hypersensitivity reaction should be asked to return the remaining **QULAM-CO** tablets to the pharmacy.
- patients who have stopped **QULAM-CO** 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 **QULAM-CO** 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.

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of abacavir as abacavir sulphate and 300 mg lamivudine.

Sugar free.

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange coloured, modified capsule shaped, biconvex, film coated tablets debossed with "I 60" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QULAM-CO is a combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age, weighing at least 40 kg.

4.2 Posology and method of administration

Posology

Patients should be stabilised on individual medicines before being switched over to **QULAM-CO**.

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

QULAM-CO should not be administered to adults or adolescent patients who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

QULAM-CO is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 50 ml/min or with mild hepatic impairment. Separate preparations of abacavir or lamivudine should be administered in cases where discontinuation or dose adjustment is indicated. In these cases, the medical practitioner should refer to the individual product information for these medicines.

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Adults and adolescents weighing at least 40 kg:

The recommended dose of **QULAM-CO** in adults and adolescents weighing 40 kg or more is one tablet once daily.

Children weighing less than 40 kg:

QULAM-CO is not recommended for treatment of children weighing less than 40 kg, as the necessary dose adjustment cannot be made. Medical practitioners should refer to the individual product information for lamivudine and abacavir.

Elderly:

The pharmacokinetics of abacavir and lamivudine has not been studied in patients over 65 years of age. When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, concomitant medicines or disease.

Renal impairment:

Whilst no dosage adjustment of abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore, **QULAM-CO** is not recommended for use in patients with a creatinine clearance less than 50 ml/min (see section **5.2**).

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 **QULAM-CO**, the separate preparation of abacavir should be used when this is judged necessary. **QULAM-CO** is contraindicated in patients with moderate and severe hepatic impairment (see section **5.2**)

Method of administration:

Oral use

QULAM-CO can be taken with or without food.

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The coated tablets should not be chewed.

4.3 Contraindications

- Patients with known hypersensitivity to abacavir or lamivudine, or to any of the excipients of PRODUCT NAME.
- Patients with moderate and severe hepatic impairment.
- Children below 12 years of age (weighing less than 40 kg) as the necessary dose adjustment cannot be made.

4.4 Special warnings and precautions for use

The special warnings and precautions relevant to both abacavir and lamivudine are included in this section. There are no additional precautions and warnings relevant to **QULAM-CO**.

Hypersensitivity to abacavir (see 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 rare cases has proved fatal.

Hypersensitivity is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue QULAM-CO and MUST not be rechallenged with QULAM-CO, or any other product containing abacavir** (see section 1 NAME OF MEDICINE – Boxed warning).

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of **QULAM-CO** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea and tachypnoea, fatigue and weight loss. Suspicious biochemical features include raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

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In patients with suspicious symptoms of 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 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).

Diagnosis of lactic acidosis 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. **The above lactate values may not be applicable to paediatric patients**. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **QULAM-CO** alone or in combination.

Caution should be exercised when administering **QULAM-CO** particularly to those with known risk factors for liver disease. Treatment with **QULAM-CO** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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, 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). It is not known whether the

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neurological disorders are transient or permanent. 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 fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving **QULAM-CO**.

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

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 blood 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:

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease) have also been reported as immune reconstitution syndrome reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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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.

Patients co-infected with hepatitis B or C virus*:*

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 professional information for these medicines. Patients co-infected with HIV and HBV who discontinue **QULAM-CO** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Clinical study and marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (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 **QULAM-CO** is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Myocardial Infarction*:*

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In a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction.

As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

***Opportunistic infections**:*

Patients receiving **QULAM-CO** may develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

Transmission of infection:

Patients should be advised that current antiretroviral therapy, including **QULAM-CO**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Weight and metabolic parameters:

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Risk of virological failure:

- Triple nucleoside therapy: There have been reports of a high rate of virological failure, and of emergence of resistance at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil fumarate as a once daily regimen.
- The risk of virological failure with **QULAM-CO** might be higher than with other therapeutic options (see section 5.1).

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4.5 Interaction with other medicines and other forms of interaction

As **QULAM-CO** contains abacavir and lamivudine, any interactions that have been identified with these medicines individually may occur with **QULAM-CO**. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine. Abacavir and lamivudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicines metabolised by major P_{450} enzymes.

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route of elimination is renal.

Interactions relevant to abacavir:

Ethanol - The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41 %. Given the safety profile of abacavir, these findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Methadone - In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35 % reduction in abacavir C_{max} and a one hour delay in T_{max}, but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22 %. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

Interactions relevant to lamivudine:

Trimethoprim - Administration of trimethoprim/sulphamethoxazole 160 mg/ 800 mg (co-trimoxazole) causes a 40 % increase in lamivudine exposure because of the trimethoprim component. However,

VR

unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see **4.2**). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

Zalcitabine- Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. **QULAM-CO** is therefore, not recommended to be used in combination with zalcitabine.

Emtricitabine– Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines 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.

The list below should not be considered exhaustive but is representative of the classes studied.

Medicines by Therapeutic Area	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINES.		
Didanosine /Abacavir	Interaction not studied.	No dosage adjustment necessary.
Didanosine/Lamivudine	Interaction not studied.	
Zidovudine/Abacavir	Interaction not studied.	
Zidovudine/Lamivudine Zidovudine 300 mg single dose Lamivudine 150 mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	

Emtricitabine/Lamivudine		Due to similarities, **QULAM-CO** should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
ANTI-INFECTIVE PRODUCTS.		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/ Abacavir	Interaction not studied.	No **QULAM-CO** dosage adjustment necessary. When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis Jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided
Trimethoprim/sulfamethoxazole (Co-trimoxazole) /Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	
ANTIMYCOBACTERIALS.		
Rifampicin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Rifampicin/Lamivudine	Interaction not studied.	
ANTICONVULSANTS.		

Phenobarbitone/ Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenobarbitone/ Lamivudine	Interaction not studied.	
Phenytoin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment. Monitor phenytoin concentrations.
Phenytoin/Lamivudine	Interaction not studied.	
ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	
Cimetidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	
CYTOTOXICS.		
Cladribine/Lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the	Therefore, the concomitant use of lamivudine with cladribine is

VR

	intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine.	not recommended (see section **4.4**).
OPIOIDS		
Methadone/Abacavir (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 %	No **QULAM-CO** dosage adjustment necessary. Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Lamivudine	Interaction not studied.	
RETINOIDS		
Retinoid compounds (e.g. isotretinoin) /Abacavir	Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dosage adjustment.
Retinoid compounds (e.g. isotretinoin) /Lamivudine No drug interaction studies	Interaction not studied.	
MISCELLANEOUS		

VR

Ethanol/Abacavir (0.7 g/kg single dose/600 mg single dose)	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dosage adjustment necessary
Ethanol/Lamivudine	Interaction not studied.	
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)/ Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14 %; 32 %; 36 % C_{max} ↓ 28 %; 52 %, 55 %.	When possible, avoid chronic coadministration of **QULAM-CO** with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; CL/F = apparent oral clearance

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **QULAM-CO** in human pregnancy has not been established.

QULAM-CO should not be used during pregnancy and lactation since teratogenicity and/or foetal toxicity cannot be excluded.

VR

Lactation

Lamivudine is excreted in human milk at similar concentrations to those found in serum. It is expected that abacavir will also be secreted into human milk. Therefore, mothers on treatment with **QULAM-CO** should not breastfeed their babies. HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, the local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

Fertility

Studies in animals showed that neither abacavir nor lamivudine had any effect on fertility (see section **5.3**).

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of **QULAM-CO** on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of these medicines. The clinical status of the patient and the adverse event profile of **QULAM-CO** should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

QULAM-CO contains abacavir and lamivudine, therefore the adverse events associated with these may be expected.

Many of the adverse events listed occur frequently (headache, nausea, abdominal pain, vomiting, and diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If **QULAM-CO** has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see

VR

Special considerations following an interruption of **QULAM-CO** therapy in section 1 NAME OF MEDICINE – Boxed warning).

Tabulated list of adverse reactions:

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders	--	Less frequent: Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia
Immune system disorders	Frequent: Medicine hypersensitivity	Less frequent: Angioedema
Metabolism and nutrition disorders	Frequent: Anorexia Less frequent: Lactic acidosis Frequency unknown: hyperlactataemia	Less frequent: Lactic acidosis Frequency unknown: hyperlactataemia
Nervous system disorders	Frequent: Headache	Frequent: Headache, insomnia. Less frequent: Cases of peripheral neuropathy (or paraesthesia) have been reported
Respiratory, thoracic and mediastinal disorders	--	Frequent: Cough, nasal symptoms
Gastrointestinal disorders	Frequent: Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration Less frequent: Pancreatitis has been reported, but a causal	Frequent: Nausea, vomiting, upper abdominal pain, diarrhoea Less frequent: Rises in serum amylase. Cases of pancreatitis have been

VR

	relationship to abacavir treatment is uncertain	Reported
Hepatobiliary disorders	--	Less frequent: Transient rises in liver enzymes (AST, ALT), hepatitis
Skin and subcutaneous tissue disorders	Frequent: Rash (without systemic symptoms) Less frequent: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Less frequent: Rash, alopecia
Musculoskeletal and connective tissue disorders	--	Frequent: Arthralgia, muscle disorders Less frequent: Rhabdomyolysis
General disorders and administration site conditions	Frequent: Fever, lethargy, fatigue	Frequent: Fatigue, malaise, fever

Description of Selected Adverse Reactions

Hypersensitivity (see section 1 NAME OF MEDICINE - Boxed warning and see section 4.4): Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in at least 10 % of patients with a hypersensitivity reaction are in bold text.

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. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin and subcutaneous tissue disorders: **Rash** (usually maculopapular or urticarial).

VR

Gastrointestinal disorders: **Nausea, vomiting, diarrhoea, abdominal pain,** mouth ulceration.

Respiratory, thoracic and mediastinal disorders: **Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure.

General disorders and administrative site conditions: **Fever, fatigue, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Nervous system disorders: **Headache**, paraesthesiae.

Blood and the lymphatic system disorders: Lymphopaenia.

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.

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. 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).

For details of clinical management in the event of a suspected abacavir HSR see section 1 NAME OF MEDICINE - Boxed warning.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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.

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4.9 Overdose

Symptoms and Signs:

No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as side effects.

Treatment:

If overdose occurs the patient should be monitored for evidence of toxicity and standard supportive treatment applied 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A, 20.2.8 Antiviral agents.

ATC code: J05AR02

Abacavir and lamivudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs) and are potent, 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. 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.

The antiviral activity of abacavir in cell culture was not antagonised when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

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HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. Studies *in vitro* indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight-fold increase in IC_{50} over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), is unlikely. Reduced susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors.

Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

5.2 Pharmacokinetic properties

Absorption:

Abacavir and lamivudine are rapidly and well absorbed following oral administration. 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 1,5 hours and 1,0 hours for abacavir and lamivudine respectively. 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

VR

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:

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 l/kg respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~49 %) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36 %). This indicates a low likelihood for interactions with other medicines through plasma protein binding displacement.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The observed values of the peak concentrations are 9-fold greater than the IC_{50} of abacavir of 0,08 µg/ml or 0,26 µM when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12 %. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism:

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:

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The mean half-life of abacavir is about 1,5 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 observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 l/h/kg, predominantly by renal clearance (greater than 70 %) via the organic cationic transport system.

Special Patient Populations:

Hepatically impaired - Pharmacokinetic data has been obtained for abacavir and lamivudine alone. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild 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 is likely to 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 has 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. **QULAM-CO** is therefore contraindicated in patients with moderate and severe hepatic impairment.

Data obtained for lamivudine in patients with moderate to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

Renally impaired - Pharmacokinetic data have been obtained for abacavir and lamivudine alone. Abacavir is primarily metabolised by the liver, with approximately 2 % of abacavir excreted unchanged

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in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction is required for patients with creatinine clearance of less than 50 ml/min, therefore the separate preparation of lamivudine should be used to treat these patients.

5.3 Preclinical safety data

There are no data available on the effects of the combination of abacavir and lamivudine in animals.

Mutagenicity and carcinogenicity

While the clinical relevance of the findings from the mutagenicity and carcinogenicity studies is unknown, the data obtained suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Repeat-dose toxicity

The clinical relevance of findings from studies on repeat-dose toxicity has not been determined.

Reproductive toxicology

A fertility study performed in rats has shown that abacavir and lamivudine had no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, povidone. The tablets are coated with coating made up of hydroxypropyl

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methylcellulose, polyethylene glycol, polysorbate, titanium dioxide and FD & C yellow no. 6 aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Keep in original packaging until required for use.

Keep the container tightly closed and in the carton until required for use.

Keep the blister in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE container

Tablets are packed in a 75 ml round white HDPE container with 38 mm neck finish, closed with a white 38 mm child resistant closure with HS 123 white printed liner, packed in an outer carton. Each HDPE container contains a 1 g silica gel sachet.

Pack sizes include 28 or 30 tablets.

Not all packs and pack sizes are necessarily marketed.

Blister pack

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Tablets are packed in a blister containing cold form laminate 25 µm OPA/45 µm aluminium foil/60 µm PVC as the forming material and plain 25 µm aluminium foil with 6-8 gsm heat seal lacquered as the lidding material, packed in a pre-printed carton.

Pack sizes include 28 or 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

QULAM-CO: 55/20.2.8/0077

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 April 2022

10. DATE OF REVISION OF THE TEXT

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