PROFESSIONAL INFORMATION FOR QUADRIMUNE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

QUADRIMUNE, oral granules in capsule.

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF LAMIVUDINE ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4).

Hypersensitivity to abacavir

Abacavir, contained in QUADRIMUNE, 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 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.

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. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

Clinical description

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. Most 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, and 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 healthcare provider immediately

If a hypersensitivity reaction is diagnosed, QUADRIMUNE must be discontinued immediately. QUADRIMUNE, or any other medicine containing abacavir, must never be restarted following a hypersensitivity reaction, as more severe symptoms may 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, QUADRIMUNE should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g. respiratory diseases, flu-like illness, gastro-enteritis or reactions to other medicines). QUADRIMUNE, or any other medicine containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s). An Alert Card with information for the patient about the hypersensitivity reaction is included in the QUADRIMUNE pack.

Special considerations following an interruption of QUADRIMUNE therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with QUADRIMUNE has been discontinued and restarting therapy 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, QUADRIMUNE or any other medicine containing abacavir should not be restarted. There have been infrequent reports of hypersensitivity reactions 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 QUADRIMUNE 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 QUADRIMUNE, this must be done only if medical care can be readily accessed by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of QUADRIMUNE in patients of unknown HLA-B*5701 status who have previously tolerated QUADRIMUNE. Re-initiation of QUADRIMUNE 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 reactions. Therefore, any patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir must contact their healthcare provider immediately.**
- **Patients who are hypersensitive to abacavir should be reminded that they must never take QUADRIMUNE or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.**

- **To avoid restarting QUADRIMUNE, patients who have experienced a hypersensitivity reaction to abacavir should be asked to return the remaining QUADRIMUNE to the pharmacy.**
- **Patients who have stopped QUADRIMUNE for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their healthcare provider before restarting.**
- **Each patient should be reminded to read the professional information included in the QUADRIMUNE pack. They should always be reminded of the importance of removing the Alert Card included in the pack and keeping it with them.**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains oral granules made up of abacavir sulfate equivalent to 30 mg abacavir, lamivudine 15 mg, lopinavir 40 mg and ritonavir 10 mg.

Contains sugar: sucrose 39,5 mg.

Contains sweeteners: aspartame 3 mg and saccharin sodium 3 mg per capsule.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Oral granules in a capsule.

White to off white coloured blend filled in capsule of size “00” having white opaque body spin printed with 3TC-ABC in black ink and brown opaque cap spin printed with LPV-RTV in black ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

QUADRIMUNE is a fixed dose combination medicine containing two nucleoside analogues (abacavir and lamivudine) and two protease inhibitors (lopinavir and ritonavir), indicated for the treatment of HIV-1 infection in children aged ≥ 3 months, weighing ≥ 3 to ≤ 19,9 kg (WHO weight band 1 (WB1), WB 2, WB 3 and WB 4) , and stabilised on concomitant use of the actives as separate formulations before switching to the fixed dose combination if similar doses of the actives can be achieved with QUADRIMUNE.

4.2. Posology and method of administration

Patients should be screened for the HLA-B*5701 allele prior to initiating therapy with QUADRIMUNE (see **boxed warning**).

Posology:

Table 1: QUADRIMUNE should be administered twice daily with food according to weight band as follows:

Weight (in kg)	**Number of capsules to be administered**	
	In the morning	**In the evening**
3,0 to 5,9	2	2
6,0 to 9,9	3	3
10, 0 to 13,9	4	4
14,0 to 19,9	5	5

QUADRIMUNE should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

Dose adjustment

In case of concomitant therapy with efavirenz or nevirapine, a dose increase of lopinavir and ritonavir may be required. However, precise dose titration will not be possible with QUADRIMUNE. Thus, it is recommended that other formulation of individual components be used in this situation.

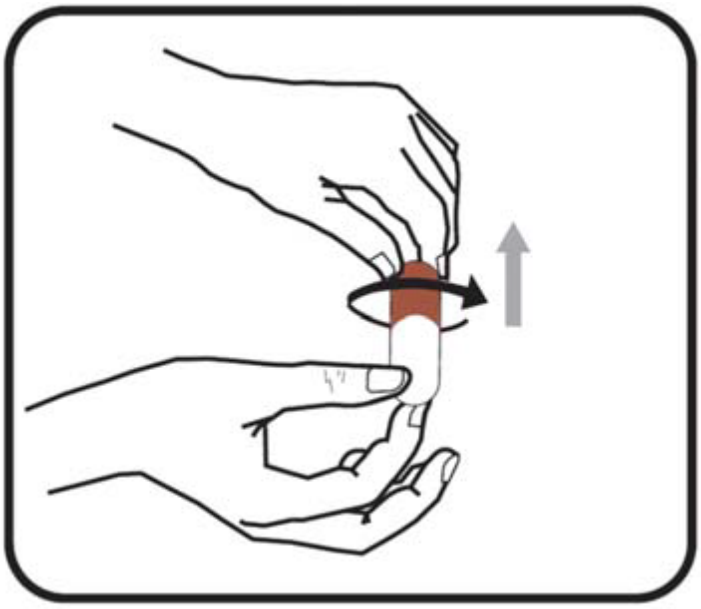
Method of administration:

Caution: Capsules should not be swallowed whole.

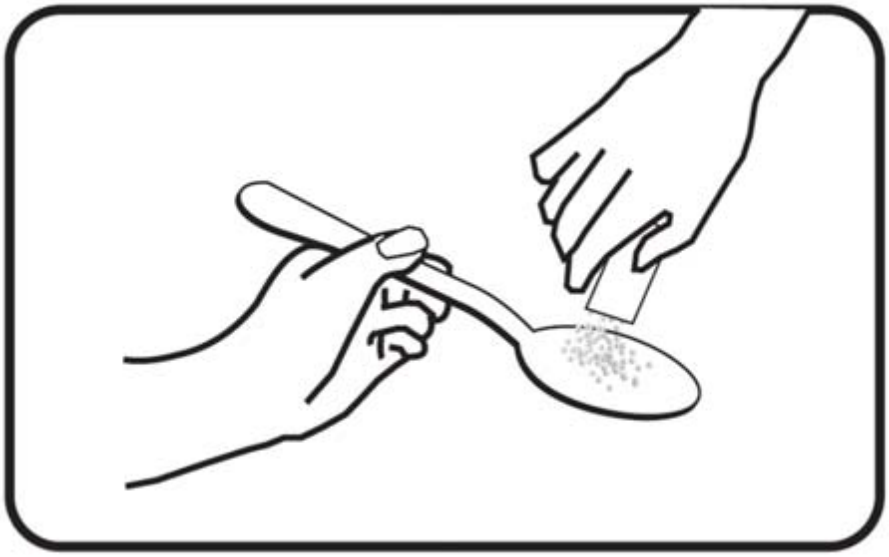
Contents of QUADRIMUNE capsules should be administered with age-appropriate soft food/liquid, as described below.

Method of administration with milk/drinking water:

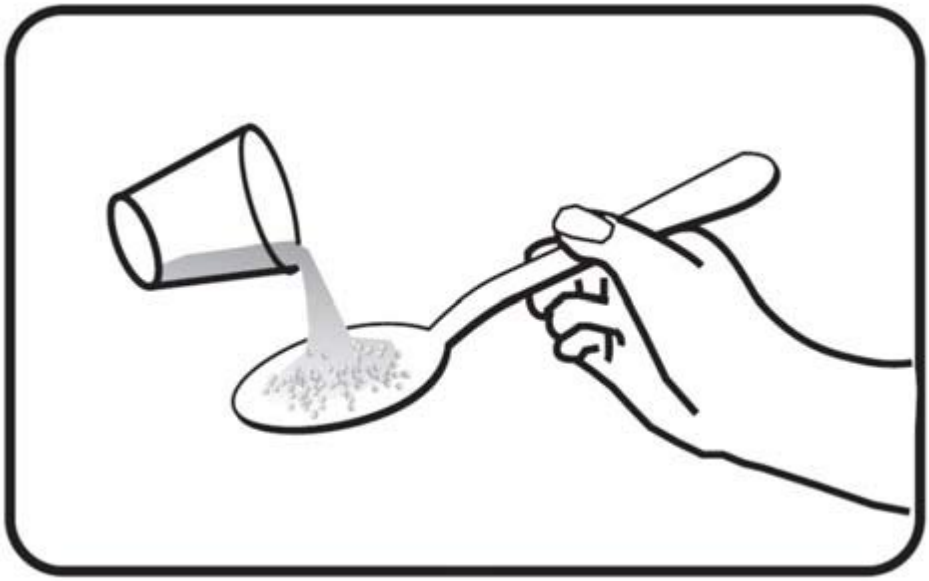
- Obtain the prescribed number of capsules needed for a dose.
- Dose the required number of capsules one by one.
- Hold one capsule vertically with the brown cap at the top and white body at the bottom and then gently tap on top of the capsule. Open the capsule by gently twisting and pulling up the cap.



- Pour the contents of capsule into a spoon.



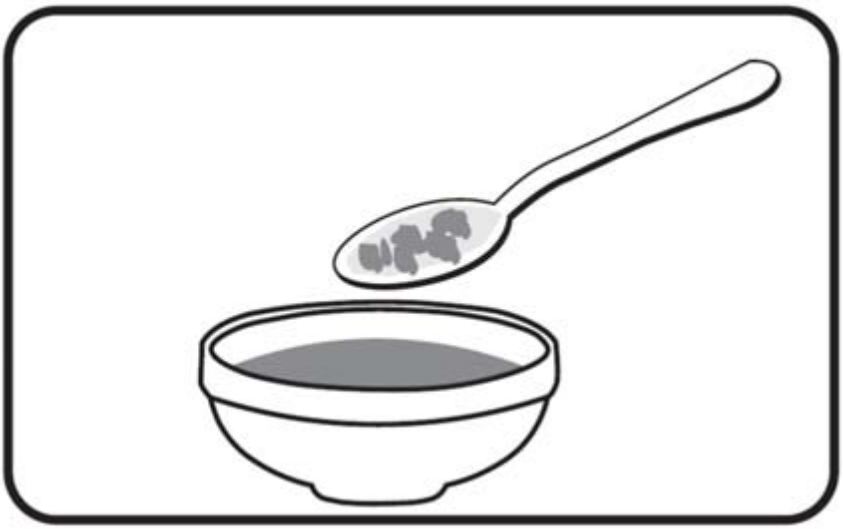
- Add milk/drinking water to the spoon till the spoon fills and feed to the child immediately.



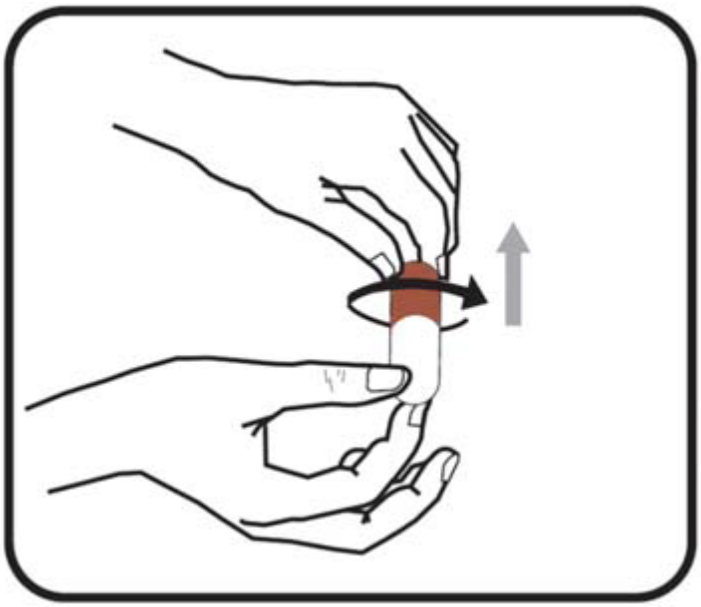
- Repeat this step for the prescribed number of capsules. Additional milk/drinking water can be taken after each dose if required.

Method of administration with soft food (e.g. porridge or mashed fruit):

- Prepare porridge/ fruit and cool to room temperature.
- Obtain the prescribed number of capsules needed for a dose.
- Dose the required number of capsules one by one.
- Take a small amount of porridge or fruit on the spoon.



- Hold one capsule vertically with the brown cap at the top and white body at the bottom and then gently tap on top of the capsule. Open the capsule by gently twisting and pulling up the cap.



- Pour the contents of capsule on the spoon containing porridge / fruit and feed to the child immediately. The porridge/ fruit with the drug sprinkled on top should be swallowed immediately and should not be stored for future use.

- Repeat this step for the prescribed number of capsules.
- Administration of the required dose should be followed by more food or drinking water/ milk, to ensure that no granules remain in the mouth.

4.3. Contraindications

QUADRIMUNE is contraindicated in:

- Patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urticaria, angioedema) to abacavir, lamivudine, lopinavir, ritonavir or any of the ingredients of QUADRIMUNE listed on **section 6.1**.
- Patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C) (see **section 4.4**).

- Combination with medicines that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions (see **sections 4.5** and **5.2**).
    - Alpha 1- adrenoreceptor antagonist: alfuzosin.
    - Antianginal: ranolazine.
    - Antidysrhythmic: dronedarone.
    - Antibiotics: fusidic acid.
    - Anticancer: neratinib.
    - Anti-gout: colchicine in patients with renal and/or hepatic impairment.
    - Antihistamine: astemizole
    - Antipsychotics: blonanserin, lurasidone,pimozide, quetiapine
    - Ergot derivatives: Ergotamine, dihydroergotamine, ergonovine, and methylergonovine.
    - GI Motility medicine: cisapride.
    - Hepatitis C direct acting antiviral: elbasvir/grazoprevir.
    - HMG-CoA reductase inhibitors: lovastatin and simvastatin.
    - Long acting beta-adrenoceptor agonist: salmeterol.
    - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide.
    - PDE5 inhibitor: sildenafil when used for the treatment of pulmonary arterial hypertension.
    - Sedative/ hypnotics: triazolam and midazolam.
- Combination with medicines that are potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance (see **sections 4.5** and **5.2**):
    - Antimycobacterial: rifampin.
    - Herbal products: St. John's Wort (*Hypericum perforatum*).

- Pregnancy and lactation (see **section 4.6**).

4.4. Special warnings and precautions for use

Hypersensitivity to abacavir

Refer to section boxed warning included under **section 1** and side effects described in **section 4.8**.

Some patients with the HLA-B*5701 allele developed abacavir-associated hypersensitivity reactions, which were fatal in some cases. Hypersensitivity is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. Patients who develop a hypersensitivity reaction must discontinue QUADRIMUNE and must not be rechallenged with QUADRIMUNE, or any other product containing abacavir.

Medicine interactions

Anti-mycobaterials

Rifampicin: QUADRIMUNE should not be co-administered with rifampicin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (see **section 4.5**).

Bedaquiline: co-administration of bedaquiline with strong CYP3A4 inhibitors (e.g.: Lopinavir and ritonavir contained in QUADRIMUNE) may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions (see **section 4.5**). Bedaquiline must be used cautiously with QUADRIMUNE, only if the benefit of co-administration outweighs the risk.

Delamanid: co-administration of delamanid with a strong inhibitor of CYP3A4 (lopinavir/ritonavir contained in QUADRIMUNE) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with

QUADRIMUNE is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **section 4.5**).

Corticosteroids

Concomitant use of lopinavir/ritonavir as contained in QUADRIMUNE and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone, or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Concomitant use of QUADRIMUNE and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when lopinavir / ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide or injectable triamcinolone. (see **section 4.5**).

PDE5 inhibitors

Co-administration of QUADRIMUNE with avanafil is not recommended.

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving QUADRIMUNE. Co-administration of QUADRIMUNE with these medicines is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, and prolonged erection.

Tadalafil: use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events.

Vardenafil: use vardenafil with caution at reduced doses of no more than 2,5 mg every 72 hours with increased monitoring for adverse events.

HMG-CoA reductase inhibitors

Caution should be exercised if HIV protease inhibitors, including lopinavir / ritonavir contained in QUADRIMUNE, are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolised by the CYP3A4 pathway (e.g., atorvastatin), as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis (see **section 4.5**).

Tipranavir

The concomitant administration of QUADRIMUNE and tipranavir is not recommended due to significant decreases in lopinavir exposure.

Lactic acidosis / hyperlactataemia

Long-term use of QUADRIMUNE can result in potentially fatal lactic acidosis because of mitochondrial dysfunction. Symptomatic hyperlactataemia and lactic acidosis are not frequent. 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.

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

- Lactate 2 to 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis (NRTIs).
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate (< 20mmol/L): Stop NRTIs and change treatment option. Once

serum 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 serum lactate level. Antiretroviral therapy should be stopped in any patient with a raised serum 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 serum 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 QUADRIMUNE alone or in combination. Caution should be exercised when administering QUADRIMUNE to any patient and particularly to those with known risk factors for liver disease. Treatment with QUADRIMUNE 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).

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 above) 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 these 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 signs and symptoms.

Pancreatitis

Pancreatitis has been observed in patients receiving lopinavir/ritonavir therapy, such as contained in QUADRIMUNE including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to QUADRIMUNE has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during QUADRIMUNE therapy.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of QUADRIMUNE is increased due to decreased clearance. The dose of QUADRIMUNE should therefore be adjusted.

Liver disease

Use of QUADRIMUNE can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of QUADRIMUNE has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection

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 QUADRIMUNE 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.

Discontinuation of QUADRIMUNE therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

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 (IRIS)

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 pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Diabetes mellitus/ hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy (like lopinavir and ritonavir as contained in QUADRIMUNE). Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic medicines for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established. Consideration should be given to the monitoring of blood glucose.

Opportunistic infections

Patients receiving QUADRIMUNE may still 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. Regular monitoring of viral load and CD4 counts needs to be done.

Risk of transmission to others

Patients should be advised that QUADRIMUNE 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.

Cardiovascular events

Although the available data from clinical and 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 QUADRIMUNE, action should be taken to minimise 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.

Myocardial infarction

Use of abacavir in combination with other antiretroviral therapy (as in QUADRIMUNE) has been associated 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 QUADRIMUNE, and action taken to minimise all modifiable risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus and smoking).

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.

Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of QUADRIMUNE therapy on the efficacy of subsequently administered protease inhibitor is unknown.

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors such as QUADRIMUNE was continued or reintroduced. Neither a causal relationship nor a mechanism of action between protease inhibitor therapy and these events has been established.

PR Interval Prolongation

Protease inhibitors have been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Infrequent reports of second or third degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported. QUADRIMUNE should be used with caution in such patients.

Lipid elevations

Protease inhibitors treatment as contained in QUADRIMUNE has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be

performed prior to initiating QUADRIMUNE therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

Carcinogenicity

An increased incidence of malignant and non-malignant tumours occurred when abacavir (contained in QUADRIMUNE) was administered orally in rats and mice. The carcinogenic potential is not known in humans. However, it is thought that the potential clinical benefit outweighs the clinical carcinogenic risk in humans.

PR interval prolongation:

Lopinavir and ritonavir have been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving medicines known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. QUADRIMUNE should be used with caution in such patients.

Excipients

QUADRIMUNE contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take QUADRIMUNE.

QUADRIMUNE contains aspartame, therefore it is not suitable for patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Abacavir

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for medicine interactions involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme.
It has also been shown *in vitro* not to interact with medicines that are metabolised by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies.

Retinoids: retinoid compounds such as isotretinoin are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Lamivudine

3TC is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicines administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic transport system e.g., trimethoprim. Other active substances (e.g., ranitidine, cimetidine) are eliminated only in part by the mechanism and were shown not to interact with lamivudine.

Zalcitabine: lamivudine, contained in QUADRIMUNE, may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. QUADRIMUNE is therefore not recommended to be used in combination with zalcitabine.

Trimethoprim / sulphamethoxazole: Administration of trimethoprim / sulphamethoxazole 160 mg/ 800 mg (co-trimoxazole) causes a 40 % increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of QUADRIMUNE is necessary (see **section 4.2**). QUADRIMUNE has no effect on the pharmacokinetics of co-trimoxazole. The effect of co-administration of QUADRIMUNE with higher doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

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. Therefore, QUADRIMUNE should not be co-administered with emtricitabine.

Ganciclovir or foscarnet:

Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended until further information is available.

Lopinavir/ritonavir component of QUADRIMUNE

Lopinavir/ritonavir is a potent inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of QUADRIMUNE and medicines primarily metabolised by CYP3A (e.g. dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors may result in increased plasma concentrations of the other medicines that could increase or prolong their therapeutic and adverse effects. Medicines that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to

large increases in AUC (greater than 3-fold) when co-administered with QUADRIMUNE. Medicines that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in **section 4.3**.

QUADRIMUNE is metabolised by CYP3A. Co-administration of QUADRIMUNE and medicines that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect. Although not noted with concurrent ketoconazole, co-administration of QUADRIMUNE and other medicines that inhibit CYP3A may increase lopinavir plasma concentrations.

Antiretroviral medicines

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Tenofovir

A study has shown that QUADRIMUNE increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving QUADRIMUNE and tenofovir should be monitored for tenofovir-associated adverse events. All increased creatinine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported particularly when protease inhibitors are given in combination with NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

Results from a study in HIV-positive paediatric subjects revealed a decrease in lopinavir concentrations during nevirapine co-administration. The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric subjects and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic interaction is unknown. For patients with extensive protease inhibitor experience, phenotypic or genotypic evidence of significant loss

of sensitivity toward lopinavir, QUADRIMUNE dosage increase should be considered when co-administered with nevirapine.

QUADRIMUNE should not be administered once daily in combination with nevirapine.

Efavirenz

Efavirenz induces the activity of CYP3A and thus has the potential to decrease plasma concentrations of other protease inhibitors when used in combination with QUADRIMUNE. QUADRIMUNE should not be administered once daily in combination with efavirenz.

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

Etravirine

Concomitant use of QUADRIMUNE with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine prescribing information.

Rilpivirine

Concomitant use of QUADRIMUNE with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine prescribing information.

Protease inhibitors

Amprenavir

QUADRIMUNE is expected to increase concentrations of amprenavir (amprenavir 750 mg BID plus lopinavir / ritonavir produces increased AUC, similar C_{max}, increased C_{min}, relative to amprenavir 1200 mg BID).

Co-administration of QUADRIMUNE and amprenavir resulted in decreased concentrations of lopinavir (see **section 4.2**). The dose of QUADRIMUNE may need to be increased during co-administration of amprenavir, particularly in patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir. QUADRIMUNE should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that co-administration of lopinavir / ritonavir, such as contained in QUADRIMUNE with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and QUADRIMUNE with respect to safety and efficacy have not been established.

Indinavir

QUADRIMUNE is expected to increase concentrations of indinavir (indinavir 600 mg BID plus lopinavir / ritonavir produces similar AUC, decreased C_{max}, increased C_{min} relative to indinavir 800 mg TID). The dose of indinavir may need to be decreased during co-administration of QUADRIMUNE. QUADRIMUNE once daily has not been studied in combination with indinavir.

Nelfinavir

QUADRIMUNE is expected to increase concentrations of nelfinavir and increase M8 metabolite of nelfinavir (nelfinavir 1000 mg BID plus lopinavir / ritonavir produces similar AUC, similar C_{max}, increased C_{min} relative to nelfinavir 1250 mg BID). Co-administration of QUADRIMUNE and nelfinavir resulted in decreased concentrations of lopinavir (see **section 4.2**). The dose of

QUADRIMUNE may need to be increased when co-administered with nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to lopinavir (see **section 4.2**). QUADRIMUNE should not be administered once daily in combination with nelfinavir.

Ritonavir

Co-administration of lopinavir / ritonavir, as contained in QUADRIMUNE, with an additional 100 mg ritonavir twice daily, resulted in increased lopinavir exposure.

Saquinavir

QUADRIMUNE is expected to increase concentrations of saquinavir (saquinavir 800 mg BID plus lopinavir / ritonavir produces increased AUC, increase C_{max}, increased C_{min} relative to saquinavir 1200 mg TID). The dose of saquinavir may need to be decreased when co-administered with QUADRIMUNE BID. QUADRIMUNE once daily has not been studied in combination with saquinavir.

HIV CCR5 – antagonist

Maraviroc

Concurrent administration of maraviroc with QUADRIMUNE will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with QUADRIMUNE BID. For further details, see complete prescribing information for maraviroc.

Hepatitis C direct acting antivirals

Boceprevir

Concomitant administration of boceprevir and lopinavir / ritonavir (as in QUADRIMUNE) resulted in reduced boceprevir and lopinavir steady-state exposure. Therefore, coadministration is not recommended.

Glecaprevir / pibrentasvir

Concomitant administration of glecaprevir / pibrentasvir and lopinavir/ritonavir (as in QUADRIMUNE) is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.

Ombitasvir/ paritaprevir/ ritonavir and dasabuvir

Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with QUADRIMUNE, therefore, co-administration is not recommended.

Simeprevir

Concomitant use of QUADRIMUNE and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer QUADRIMUNE and simeprevir.

Sofosbuvir/ velpatasvir/ voxilaprevir

Concomitant administration of sofosbuvir/ velpatasvir/ voxilaprevir and QUADRIMUNE is not recommended due to the potential for increased toxicity, which may negatively impact compliance.

Telaprevir

Concomitant administration of telaprevir and lopinavir / ritonavir (as in QUADRIMUNE) resulted in reduced telaprevir steady-state exposure, while the lopinavir steady state exposure was not affected.

Other medicines:

Analgesics

Fentanyl

QUADRIMUNE inhibits CYP3A4 and as a result, it is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with QUADRIMUNE.

Methadone

Lopinavir / ritonavir was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Antidysrhythmics

Amiodarone, bepridil, dronedarone, lidocaine (lignocaine) and quinidine

Concentrations may be increased when co-administered with QUADRIMUNE. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Digoxin

A literature report has shown that co-administration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when co-administering QUADRIMUNE with digoxin, with appropriate monitoring of serum digoxin levels.

Anti-cancer medicines

Abemaciclib, dasatinib, ibrutinib, neratinib, nilotinib, venetoclax, vincristine, vinblastine

Serum concentrations of the anti-cancer medicines may be increased when co-administered with QUADRIMUNE resulting in the potential for increased adverse events usually associated with these anticancer medicines.

Co-administration of venetoclax or ibrutinib with QUADRIMUNE could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. For venetoclax, ibrutinib, nilotinib, and dasatinib, refer to their prescribing information for dosing instructions.

Anticoagulants

Warfarin

Warfarin concentrations may be affected when co-administered with QUADRIMUNE. It is recommended that INR (international normalised ratio) be monitored.

Rivaroxaban

Co-administration of rivaroxaban and QUADRIMUNE may increase rivaroxaban exposure which may increase the risk of bleeding.

Antidepressants

Bupropion

Concurrent administration of bupropion with QUADRIMUNE will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).

Trazodone

Concomitant use of ritonavir (as in QUADRIMUNE) and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been

observed. If trazodone is used with a CYP3A4 inhibitor such as QUADRIMUNE, the combination should be used with caution and a lower dose of trazodone should be considered.

Anticonvulsants

Phenobarbital, phenytoin and carbamazepine

These medicines are known to induce CYP3A4 and may decrease lopinavir concentrations. QUADRIMUNE should not be administered once daily in combination with phenobarbital, phenytoin or carbamazepine.

In addition, co-administration of phenytoin and lopinavir/ritonavir resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administration with QUADRIMUNE.

Lamotrigine and valproate

Caution is recommended as co-administration of lopinavir / ritonavir and either of these medicines was associated with reduction in exposure of the anticonvulsant and 50 % reduction in lamotrigine exposure.

A dose increase of the anticonvulsant may be needed when co-administered with

Lopinavir / ritonavir and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.

Antigout medicines

Concentrations of colchicine are expected to increase when co-administered with

QUADRIMUNE. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (see **section 4.3**). Refer to the colchicine professional information for prescribing information.

Anti-infectives

Antifungals

Ketoconazole and itraconazole

Ketoconazole and itraconazole may have their serum concentrations increased by QUADRIMUNE. High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

Co-administration of ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39 %; therefore, co-administration of QUADRIMUNE and voriconazole should be avoided, unless an assessment of the benefit/ risk to the patient justifies the use of voriconazole.

Anti-bacterials

Clarithromycin

Moderate increases in clarithromycin AUC are expected when co-administered with QUADRIMUNE. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Anti-mycobacterials

Rifabutin: when rifabutin and lopinavir / ritonavir, such as contained in QUADRIMUNE were co-administered for ten days, rifabutin (parent medicine and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3,5- and 5,7-fold, respectively. Based on these data, a rifabutin dose reduction of 75 % (i.e. 150 mg every other day or three times per week) is recommended when administered with QUADRIMUNE. Further dose reduction of rifabutin may be necessary.

Rifampicin: due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with QUADRIMUNE (see **section 4.3**). The use of rifampicin with standard dose QUADRIMUNE may lead to loss of virologic response and possible resistance to QUADRIMUNE or to the class of protease inhibitors or other co-administered antiretroviral medicines. Co-administration of rifampicin with 800/ 200 mg lopinavir / ritonavir BID resulted in decreases in lopinavir of up to 57 % and with lopinavir / ritonavir 400/ 400 mg BID resulted in decreases of up to 7 % when compared to lopinavir /ritonavir 400/ 100 mg BID dosed in the absence of rifampicin. ALT and AST elevations have been noted in studies with higher doses of lopinavir/ritonavir co-administered with rifampicin and may be dependent on the sequence of dose administration. If co-administration is being considered, QUADRIMUNE should be initiated at standard dose for approximately 10 days prior to addition of rifampicin. QUADRIMUNE dose should then be titrated upward. Close monitoring of liver function is indicated.

Bedaquiline: bedaquiline exposure is increased by co-administration with QUADRIMUNE. Therefore, QUADRIMUNE must be used cautiously with bedaquiline, only if the benefit of co-administration outweighs the risk (see **section 4.3**).

Delamanid: co-administration of delamanid with QUADRIMUNE is associated with increased exposures of delamanid and a delamanid metabolite, DM-6705. Due to the risk of QTc prolongation associated with DM 6705, if co-administration of delamanid with
QUADRIMUNE is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **section 4.3**).

Antiparasitics

Atovaquone

Decreases in the therapeutic concentration of atovaquone are possible when co-administered with QUADRIMUNE. Increases in atovaquone doses may be necessary.

Antipsychotics

Due to CYP3A inhibition by lopinavir / ritonavir concentrations of quetiapine are expected to increase. Refer to quetiapine prescribing information for dosing instructions.

Corticosteroids

Dexamethasone

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Consider alternatives to fluticasone propionate, particularly for long-term use (**section 4.3**).

Concomitant use of QUADRIMUNE and fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as budesonide, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

Consider alternatives to fluticasone propionate, budesonide and injectable triamcinolone, particularly for long-term use (see **section 4.3**).

Dihydropyridine calcium channel blockers

Felodipine, Nifedipine, Nicardipine etc.

Serum concentrations of these medicines are increased by co-administration with QUADRIMUNE.

PDE5 inhibitors

Avanafil

Co-administration of QUADRIMUNE with avanafil is expected to result in large increases in avanafil exposure and is not recommended (see **section 4.4**).

Sildenafil

Use sildenafil for the treatment of erectile dysfunction with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events (see **section 4.4**).

Concomitant use of sildenafil with QUADRIMUNE is contraindicated in pulmonary arterial hypertension (PAH) patients (see **section 4.3**).

Tadalafil

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see **section 4.4**). When tadalafil is administered for the treatment of pulmonary arterial hypertension to patients who are receiving QUADRIMUNE, refer to the tadalafil prescribing information.

Vardenafil

Use vardenafil with caution at reduced doses of no more than 2,5 mg every 72 hours with increased monitoring for adverse events (see **section 4.4**).

Herbal products

St. John's Wort (*Hypericum perforatum)*

Patients receiving QUADRIMUNE should not use products containing St. John's Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of QUADRIMUNE. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see **section 4.3**).

HMG-CoA reductase inhibitors

Lovastatin and simvastatin

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with QUADRIMUNE. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these medicines with QUADRIMUNE is contraindicated (see **section 4.3**).

Atorvastatin

Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with lopinavir / ritonavir, a mean 4,7-fold and 5,9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with QUADRIMUNE, the lowest possible doses of atorvastatin should be administered (see **section 4.4**).

Pravastatin and Fluvastatin

Results from a medicine interaction study with lopinavir / ritonavir and pravastatin reveal no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with QUADRIMUNE. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Lomitapide

Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors such as QUADRIMUNE with lomitapide is contraindicated.

Immunosuppressants

Cyclosporin, tacrolimus and Sirolimus (rapamycin) etc.

Concentrations of these medicines may be increased when co-administered with QUADRIMUNE. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilised.

Oral contraceptives or patch contraceptives

Since levels of ethinyl estradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and QUADRIMUNE are co-administered.

Vasodilating medicines

Co-administration of bosentan and lopinavir / ritonavir increased steady state bosentan maximum concentrations (C_{max}) and AUC by 6-fold and 5-fold, respectively. Refer to the bosentan prescribing information.

4.6. Fertility, pregnancy and lactation

Pregnancy

QUADRIMUNE is contraindicated during pregnancy.

Abacavir:

Safety in human pregnancy has not been established.

Abacavir should not be used during pregnancy and lactation since teratogenicity and/ or foetal toxicity cannot be excluded (see **section 4.3**).

Lamivudine:

Lamivudine has not been studied in pregnant women. However, use of NRTIs in pregnancy has been associated with mild and transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or peri-partum. The clinical relevance of elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease.

Breastfeeding:

Studies have indicated that components of QUADRIMUNE (abacavir, lamivudine and lopinavir) are excreted in breast milk. Therefore, nursing mothers should not breastfeed their children while on QUADRIMUNE therapy.

Fertility*:*

There are no data on fertility.

4.7. Effect on ability to drive and use machines

There are less frequent reports of visual impairment due to use of QUADRIMUNE. Patients need to be aware of how QUADRIMUNE affects them before engaging in potentially dangerous activities such as driving or operating machinery.

4.8. Undesirable effects

Summary of the safety profile:

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu- like illness. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or death.

Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, as contained in QUADRIMUNE, although these reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It is likely that intermittent therapy may increase the risk of developing sensitisation and therefore occurrence of clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking QUADRIMUNE regularly.

Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue QUADRIMUNE and must never be rechallenged with QUADRIMUNE, or any other medicine containing abacavir.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, abacavir, as in QUADRIMUNE, must 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).

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir, as in QUADRIMUNE, in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, 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. In both cases, if a decision is made to restart abacavir, as in QUADRIMUNE, this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir, as in QUADRIMUNE.

Many of the adverse reactions listed in the table below occur commonly (nausea, vomiting, 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 QUADRIMUNE has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicine containing abacavir, this must be done in a setting where medical assistance is readily available. Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out.

In such cases medicines containing abacavir, as in QUADRIMUNE, should be permanently discontinued.

Tabulated list of adverse reactions

The adverse reactions are listed by body system, organ class and absolute frequency.

Table 2: Side effects reported from individual molecules of QUADRIMUNE

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**
Infections and infestations			*Frequent*: upper respiratory tract infection, lower respiratory tract infection, skin infections including

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			cellulitis, folliculitis and furuncle. *Less frequent:* otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral infection, pharyngitis, flu syndrome, gastroenteritis, sialadenitis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)			*Less frequent: s*kin benign neoplasm, cyst, neoplasm.
Blood and lymphatic system disorders		*Less frequent:* neutropenia, anaemia, thrombocytopenia, pure red cell aplasia.	*Frequent*: anaemia, leucopenia, lymphadenopathy and neutropenia.
Immune system disorders	Frequent: Hypersensitivity		*Frequent*: hypersensitivity

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			including urticaria and angioedema. *Less frequent:* immune reactivation syndrome.
Endocrine disorders			*Less frequent:* hypogonadism, Cushing syndrome, hypothyroidism.
Metabolism and nutrition disorders	*Frequent*: anorexia. Hyperlactataemia Less frequent: Lactic acidosis, redistribution/accumulation of body fat	*Frequent*: hyperlactataemia. *Less frequent:* lactic acidosis (see **section 4.4**), lipodystrophy (redistribution/ accumulation of body fat (see **section 4.4**)	*Frequent*: hypercholesterolemia, hypertriglyceridemia lactic acidosis, blood glucose disorders including diabetes mellitus, hyperglycaemia, decreased appetite. *Less frequent:* avitaminosis, dehydration, increased appetite, obesity, anorexia,

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			weight gain, weight loss.
Psychiatric disorders			*Frequent*: Insomnia, anxiety. *Less frequent:* abnormal dreams, agitation, anxiety, confusion, depression, emotional lability, decreased libido, nervousness, abnormal thinking, apathy.
Nervous system disorders	*Frequent*: headache.	*Frequent*: headache. Insomnia *Less frequent:* paraesthesia, peripheral neuropathy.	*Frequent*: headache (including migraine), neuropathy including (peripheral neuropathy), dizziness, insomnia. *Less frequent:* amnesia, ataxia, encephalopathy, facial

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			paralysis, hypertonia, neuropathy, paraesthesia, peripheral neuritis, somnolence, tremor, taste loss, taste perversion, migraine, dyskinesia, cerebral infarct, convulsion, extrapyramidal syndrome.
Eye disorders			*Less frequent:* abnormal vision, eye disorders.
Ear and labyrinth disorders			*Less frequent:* tinnitus, vertigo.
Cardiac disorders			*Less frequent:* atherosclerosis, myocardial infarction, angina pectoris, atrioventricular block, tricuspid valve incompetence.

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
Vascular disorders			*Less frequent:* hypertension, thrombophlebitis, vasculitis, varicose vein, deep thrombophlebitis, vascular disorder, postural hypotension.
Respiratory, thoracic and mediastinal disorders		Frequent: cough, nasal symptoms	*Less frequent:* *d*yspnoea, rhinitis, asthma, lung oedema, increased coughing.
Gastrointestinal disorders	*Frequent*: nausea, vomiting, diarrhoea. Less frequent: Pancreatitis.	*Frequent*: nausea, vomiting, upper abdominal pain, diarrhoea. *Less frequent:* pancreatitis, rises in serum amylase.	*Frequent*: diarrhoea, nausea, pancreatitis vomiting, gastro-oesophageal reflux disease, gastroenteritis and colitis abdominal pain (upper and lower), abdominal distension, dyspepsia,

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			haemorrhoids, flatulence. *Less frequent:* gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastric ulcer, gastritis, mouth ulcerations, rectal haemorrhage, stomatitis, faecal incontinence, constipation, dry mouth.
Hepato-biliary disorders		*Less frequent:* transient rises in liver enzymes (AST, ALT).	*Frequent*: hepatitis including AST, ALT and GGT increases. *Less frequent:* cholecystitis, cholangitis, jaundice, hepatomegaly, liver

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			fatty deposit, liver tenderness.
Skin and subcutaneous tissue disorders	*Frequent:* Rash (without systemic symptoms) *Less frequent:* Erythema multiforme, Stevens- Johnson syndrome and toxic epidermal necrolysis.	*Frequent*: rash, alopecia	*Frequent*: rash including maculo-papular rash, dermatitis/ rash including eczema and seborrheic dermatitis, night sweats, pruritus, alopecia, capillaritis, vasculitis. *Less frequent:* dry skin, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, nail disorder, pruritis, seborrhoea, skin discolouration, skin

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			ulcer, face oedema, acne, sweating, skin striae.
Musculoskeletal and connective tissue disorders		*Frequent*: arthralgia, muscle disorders. *Less frequent:* rhabdomyolysis.	*Frequent*: myalgia, musculoskeletal pain including arthralgia and back pain, muscle disorders such as weakness and spasms. *Less frequent:* rhabdomyolysis, osteonecrosis.
Renal and urinary disorders			*Less frequent:* creatinine clearance decreased, nephritis, haematuria.
Reproductive system and breast disorders			*Frequent*: erectile dysfunction, menstrual disorders amenorrhoea and menorrhagia.

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			Less frequent: ejaculation disorder, breast enlargement, gynaecomastia.
General disorders and administration site conditions	*Frequent*: fever, lethargy, fatigue.	*Frequent*: fatigue, malaise, fever.	*Frequent*: fatigue including asthenia. *Less frequent:* chest pain, chest pain substernal, chills, fever, malaise, pain, peripheral oedema, medicine interaction, oedema, hypertrophy.
Investigations			Frequent: Increased triglycerides, increased total cholesterol, increased GGT, increased glucose, increased amylase, increased AST, increased ALT,

System organ class	Abacavir component	Lamivudine component	Lopinavir / ritonavir component
			abnormal liver function tests. Less Frequent: Decreased glucose tolerance, weight gain, weight loss, increased bilirubin, hormone level altered, lab test abnormal

Post-marketing data

Table 3: Post-marketing side effects reported from individual molecules of QUADRIMUNE

System organ class	Abacavir component	Lopinavir / ritonavir component
Blood and lymphatic system disorders	Lymphopenia.	
Metabolism and nutrition disorders	Hyperlactataemia Lactic acidosis (see **section 4.4**).	
Nervous system disorders	Headache, paraesthesia.	

System organ class	Abacavir component	Lopinavir / ritonavir component
Cardiac disorders		Bradydysrhythmia
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure.	
Gastrointestinal disorders	Pancreatitis, nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.	
Hepato-biliary disorders	Elevated liver function tests, hepatic failure.	Hepatitis
Skin and subcutaneous tissue disorders	Rash (maculopapular or urticarial), erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	Stevens-Johnson Syndrome and erythema multiforme.
Musculoskeletal and connective tissue disorders	Myalgia, myolysis, arthralgia, elevated creatine phosphokinase.	
Renal and urinary disorders	Elevated creatinine, renal failure.	
General disorders and administrative site conditions	Fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.	

c) Description of Selected Adverse Reactions

In clinical studies approximately 5 % of subjects receiving abacavir developed hypersensitivity reactions. Some hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions. This reaction is characterised 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.

The signs and symptoms of this hypersensitivity reaction are listed below.

Those reported in at least of 10 % of patients with hypersensitivity reactions are in bold text:

Skin and subcutaneous tissue disorders	**Rash** (usually maculopapular or urticarial)
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, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Nervous system disorders	**Headache**, paraesthesia

Blood and the lymphatic system disorders	**Lymphopenia**
Hepato-biliary disorders	**Elevated liver function tests,** hepatitis, 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, as in QUADRIMUNE, following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction 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.

Clinical Trials Experience in Paediatric Subjects

Abacavir and lamivudine

The safety database to support abacavir and lamivudine once daily in paediatric patients comes from the ARROW Trial (COL105677) in which HIV-1 infected paediatric subjects received

abacavir and lamivudine either once or twice daily. No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Lopinavir and ritonavir

The safety and pharmacokinetic profiles of lopinavir/ritonavir in paediatric patients below the age of six months have not been established. In HIV-infected patients aged six months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients.

Undesirable Effects in Paediatric Patients		
Infections and infestations	Frequent	Viral infection
Nervous system disorders	Frequent	Taste perversion
Gastrointestinal disorders	Frequent	Constipation, vomiting, pancreatitis
Hepatobiliary disorders	Frequent	Hepatomegaly
Skin and subcutaneous tissue disorders	Frequent	Rash, dry skin
General disorders and administration site conditions	Frequent	Fever
Investigations	Frequent	Increased activated partial thromboplastin time, decreased haemoglobin, decreased platelets, increased sodium, increased potassium, increased calcium, increased bilirubin, increased ALT, increased AST, increased total cholesterol, increased amylase, increased uric acid, decreased sodium, decreased potassium, decreased calcium, decreased neutrophils.

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 via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email:drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free)..

4.9. Overdose

Abacavir/ lamivudine component:

Symptoms and signs

In overdose, side effects can be precipitated and/ or be of increased severity. 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. Treatment is symptomatic and supportive. 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. Activated charcoal administration if the patient is seen within one hour after overdose.

Lopinavir / ritonavir component:

Treatment of overdose with lopinavir / ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with lopinavir / ritonavir. If indicated, elimination of unabsorbed medicine should be achieved by emesis if the patient’s level of consciousness is normal and is

seen within one hour after overdose. Administration of activated charcoal may also be used to aid in removal of unabsorbed medicine. Since lopinavir / ritonavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: 20.2.8 Antiviral medicines.

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations

ATC code: J05AR

Abacavir

Abacavir is a nucleoside analogue reverse transcriptase inhibitor that is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP) which inhibits the HIV reverse transcriptase enzyme, resulting in chain termination and interruption of the viral replication cycle. Abacavir is a selective inhibitor of HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine.

It showed synergy *in vitro* in combination with nevirapine and zidovudine and was shown to be additive in combination with didanosine, zalcitabine, lamivudine and stavudine.

Lamivudine

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. *In vitro*, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Lopinavir and ritonavir

Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases.

Ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Inhibition of HIV protease prevents cleavage of the *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Resistance

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (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.

Lamivudine-resistant variants of HIV-1 have been selected *in vitro*. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients.

Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant

to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine. Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy. The relationship between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

Cross-resistance

Patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during lopinavir/ritonavir therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir and nelfinavir.

5.2. Pharmacokinetic properties

Absorption

Abacavir

Following oral administration, abacavir is well absorbed and has absolute bioavailability of 83 %, and t_{max} 1,5 hours.

At a dosage of 300 mg twice daily, the mean steady state C_{max} of abacavir was 3,00 µg/mL, and the mean AUC over a dosing interval of 12 hours was 6,02 µg.h/mL (daily AUC of approximately 12,0 µg.h/mL). Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore, abacavir can be taken with or without food.
The steady state pharmacokinetic properties of abacavir 600 mg once daily was compared to abacavir 300 mg twice daily. Intracellular carbovir triphosphate exposures in peripheral blood mononuclear cells were higher for abacavir 600 mg once daily with respect to $AUC_{24,ss}$ (32 %, higher), $C_{max\ 24,ss}$ (99 % higher) and trough values (18 % higher), compared to the 300 mg twice daily regimen. These data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients.

Lamivudine

Adults

Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. Following oral administration, the t_{max} maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 to 1,5 µg/mL.

No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in t_{max} and reduction in C_{max} have been observed.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and

therefore no dosage adjustments are necessary. The likelihood of adverse interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

Children

The absolute bioavailability of lamivudine (approximately 58 to 66 %) was lower and more variable in paediatric patients below 12 years of age. Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

Lopinavir and ritonavir

Multiple dosing of 400/ 100 mg lopinavir/ritonavir twice daily with food for three weeks produced a mean ± SD lopinavir peak plasma concentration of 12,3 ± 5,4 µg/mL, occurring approximately four hours after administration. The mean steady-state trough concentration prior to the morning dose was 8,1 ± 5,7 µg/mL and minimum concentration within a dosing interval was 5,6 ± 4,5 µg/mL. Lopinavir AUC over a 12-hour dosing interval averaged 113,2 ± 60,5 µg.h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Administration of a single 400/ 100 mg dose of lopinavir / ritonavir under fed conditions (high-fat, 872 kcal, 56 % from fat) compared to the fasted state was associated with no significant changes in C_{max} and AUC_{inf}, therefore, lopinavir / ritonavir may be taken with or without food. Lopinavir / ritonavir has also shown less pharmacokinetic variability under all meal conditions.

Distribution

Abacavir

Following intravenous administration, the apparent volume of distribution was about 0,8 L/kg. Studies in HIV-infected patients have shown that abacavir enters the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44 %. The penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1,5 hours post dose was 0,14 µg/mL. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0,13 µg/mL at 0,5 to 1 hour after dosing, to approximately 0,74 µg/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9-fold greater than the IC_{50} of abacavir of 0,08 µg/mL or 0,26 µM.
Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (approximately 49 %) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions through plasma protein binding displacement.

Lamivudine

From intravenous studies, the mean volume of distribution is 1,3 L/kg and the mean terminal half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Limited data shows lamivudine penetrates the central nervous system and reaches the CSF. The mean ratio CSF/ serum lamivudine concentration 2 to 4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Lopinavir

At steady state, lopinavir is approximately 98 to 99 % bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/ 100 mg lopinavir / ritonavir BID, and is similar between healthy volunteers and HIV-positive patients.

Biotransformation

Abacavir

Abacavir undergoes hepatic metabolism mainly, 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 dose in the urine.

Lopinavir and ritonavir

Lopinavir has been shown to undergo oxidative metabolism in *in vitro* studies with human hepatic microsomes. Lopinavir undergoes extensive hepatic metabolism by the cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89 % of the plasma radioactivity after a single 400/100 mg lopinavir/ritonavir dose was due to parent compound. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 to 16 days.

Elimination

Abacavir

The mean half-life of abacavir is about 1,5 hours. Following multiple oral doses of abacavir 300 mg twice a day there was no significant medicine accumulation. 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.

Lamivudine

Lamivudine elimination will be affected by renal impairment, whether it is disease- or age-related. A recommended dosage regimen for patients with creatinine clearance below 50 mL/min is shown in the dosage section.

Lopinavir and ritonavir

Following a 400/ 100 mg ^{14}C-lopinavir / ritonavir dose, approximately 10,4 ± 2,3 % and 82,6 ± 2,5 % of an administered dose of ^{14}C-lopinavir can be accounted for in urine and faeces respectively, after eight days. Unchanged lopinavir accounted for approximately 2,2 and 19,8 % of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3 % of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5,98 ± 5,75 L/hr (mean ± SD, N = 19).

Special populations

Paediatrics

QUADRIMUNE must not be given to children under 3 months of age.

There are limited pharmacokinetic data for patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Hepatic impairment

QUADRIMUNE is contraindicated in patients with moderate (child-Pugh class B) to severe (Child – Pugh class C) hepatic impairment.

Abacavir and lopinavir are metabolised primarily by the liver. Abacavir resulted in a mean increase of 1,89-fold in the abacavir AUC, and 1,58-fold in the half-life of abacavir following administration in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased.

Multiple dosing of lopinavir / ritonavir 400/ 100 mg twice daily increased AUC by 30 % and C_{max} by 20 % in HIV and HCV co-infected patients with mild (child-Pugh class B) to moderate (child-Pugh class C) hepatic impairment when compared to those with normal hepatic function. Furthermore, the plasma protein binding of lopinavir was lower in both mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment compared to controls (99,09 vs 99,31 % respectively).

The safety and efficacy of lamivudine has not been established in patients with significant underlying liver disorders/diseases. No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Renal insufficiency

Dose adjustment is not necessary in patients with renally impaired function.

Abacavir undergoes hepatic metabolism, with approximately 2 % of abacavir excreted unchanged in the urine. The pharmacokinetic properties of abacavir in patients with end-stage renal disease

are similar to patients with normal renal function. Therefore, no dosage reduction is required in patients with renal impairment.

Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Lamivudine concentrations are increased in patients with moderate to severe renal impairment due to decreased clearance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The full list of inactive ingredients:

amino methacrylate copolymer,

aspartame,

colloidal silicon dioxide,

hypromellose,

microcrystalline cellulose,

saccharin sodium,

sodium starch glycolate,

starch,

stearic acid,

strawberry cream flavour permaseal,

sucrose,

vegetarian capsule.

The strawberry cream flavour permaseal is made up of

modified waxy maize starch- 1450,

nature identical flavouring substance,

natural flavouring substance,

propyleneglycol-1520

waxy maize maltodextrin.

Constituents of the vegetarian capsule:

black iron oxide (E172),

hypromellose,

red iron oxide (E172),

titanium dioxide,

yellow iron oxide (E172) and

printing ink (Opacode® Monogramming Ink S-1-8114 Black

Opacode® Monogramming Ink S-1-8115 Black).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C in the original container.

6.5. Nature and contents of container

QUADRIMUNE is marketed in packs of 120 in white HDPE containers that are fitted with lined non-CRC caps and contain one 3 g silica gel desiccant.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

55/20.2.8/0388

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 24 May 2022

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

09 September 2025