Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Abacavir, Lamivudine, Lopinavir and Ritonavir Granules 30 mg/15 mg/40 mg/10 mg

2. Qualitative and quantitative composition

Each capsule contains:
Abacavir Sulfate USP equivalent to
Abacavir.....30 mg
Lamivudine USP.....15 mg
Lopinavir USP.....40
mg

Ritonavir USP.....10 mg
Excipients with known effects
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

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

It 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 ≤19.9kg (WHO weight band 1 (WB1), WB 2, WB 3 and WB 4) , and stabilised on concomitant use of the actives as separate formulations

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before switching to the fixed dose combination if similar doses of the actives can be achieved with the drug.

WHO guideline recommendations**:**

Since 2013, the World Health Organization recommended the use of Lopinavir/ritonavir-based regimens in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) as first-line antiretroviral therapy (ART) for all children infected with HIV younger than three years, regardless of non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure.

The 2018 WHO guidelines for treating and preventing HIV infection recommended a dolutegravir (DTG)-based regimen in combination with Abacavir(ABC) and Lamivudine(3TC) as the preferred first-line regimen for children for whom approved DTG dosing is available. In the absence of appropriate DTG formulations and dosing for infants and young children, ABC + 3TC in combination with LPV/r are considered as an acceptable alternative given the superiority of LPV/r over non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens.

Till 2020, implementation of DTG based regimens in children have only been feasible among those weighing 20kgs and above among whom DTG 50 mgs tablets can be utilized, while children weighing less than 20kgs continue to be use LPV/r based regimens. ABC + 3TC in combination with LPV/r remains an important alternative regimen for use in first line among infants and young children.

4.2 Posology and method of administration

Dose recommendation

Simplified weight band dosing schedule for ABC/3TC/LPV/r 30/15/40/10mg oral granules

Table 1. Dosage Recommendation of Abacavir, Lamivudine, Lopinavir and Ritonavir Granules Based on Weight Band

The ABC/3TC/LPV/r 30/15/40/10mg oral granules should be administered twice daily with food. The table lists the number of capsules containing abacavir, lamivudine, lopinavir and ritonavir granules to be administered twice-daily, using a simplified weight band-based approach.

Weight Band	**Number of capsules containing abacavir, lamivudine, lopinavir and ritonavir granules* needed to prepare each dose**	
	AM	**PM**
3.0 kg – 5.9 kg	2	2
6.0 kg – 9.9 kg	3	3
10.0 kg – 13.9 kg	4	4
14.0 kg – 19.9 kg	5	5
20.0 kg – 24.9 kg	6	6

* without concomitant efavirenz, nevirapine or nelfinavir

The drug 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 the drug. Thus, it is recommended that other formulation of individual components be used in this situation.

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Method of administration

Capsules containing abacavir, lamivudine, lopinavir and ritonavir granules should not be swallowed whole, and should be administered with food or liquids.

Instructions for administration with milk/drinking water

I. Obtain the prescribed number of capsules needed for a dose.
II. Dose the required number of capsules one by one.
III. 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.
IV. Open the capsule by gently twisting and pulling up the cap V. Pour the contents of the capsule into a spoon.
VI. Add milk/drinking water to the spoon till the spoon fills and feed to the child immediately.
VII. Repeat this step for the prescribed number of capsules.
VIII. Additional milk/drinking water can be taken after each dose if required.

Instructions for administration with soft food (e.g. porridge or mashed fruit)

I. Prepare porridge / fruit and cool to room temperature.
II. Obtain the prescribed number of capsules needed for a dose.
III. Dose the required number of capsules one by one.
IV. Take a small amount of porridge / fruit on the spoon.
V. 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.
VI. Open the capsule by gently twisting and pulling up the cap.
VII. 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.

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VIII. Repeat this step for the prescribed number of capsules.

IX. 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

Patients with previously demonstrated clinically significant hypersensitivity (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiform, urticaria, angioedema) to abacavir, lamivudine, lopinavir, ritonavir or any of the ingredients of the drug 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 and pimozide
- Ergot derivatives: Ergotamine, dihydroergotamine, ergonovine, and methylergonovine.

- GI Motility medicine: cisapride.
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir.
- HMG-CoA deductase 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*).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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 the drug and must not be rechallenged with it, or any other product containing abacavir

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Lactic acidosis / hyperlactataemia

Long-term use of ABC/3TC/LPV/r 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 tachypnea, 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 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis (NRTIs).
- Lactate 5-10 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 ABC/3TC/LPV/r alone or in combination.

Caution should be exercised when administering ABC/3TC/LPV/r to any patient and particularly to those with known risk factors for liver disease.
Treatment with ABC/3TC/LPV/r should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or

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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 (anemia, neutropenia) and peripheral neuropathy. Some late onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). It is not known whether these neurological disorders are transient or permanent. Any fetus 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 ABC/3TC/LPV/r including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to the drug 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 the drug therapy.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of ABC/3TC/LPV/r

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is increased due to decreased clearance. The dose of ABC/3TC/LPV/r should therefore be adjusted.

Liver disease

Use of ABC/3TC/LPV/r can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ABC/3TC/LPV/r 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 ABC/3TC/LPV/r should be closely monitored with both clinical and laboratory follow-ups 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 the drug therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

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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. Autoimmune 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 ABC/3TC/LPV/r).
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

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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 ABC/3TC/LPV/r 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 ABC/3TC/LPV/r 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.

Myocardial infarction

Use of abacavir in combination with other antiretroviral therapy 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 ABC/3TC/LPV/r
, and action taken to minimize 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

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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 ABC/3TC/LPV/r 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 ABC/3TC/LPV/r 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. The drug should be used with caution in such patients.

Lipid elevations

Protease inhibitors treatment as contained in ABC/3TC/LPV/r has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride

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and cholesterol testing should be performed prior to initiating ABC/3TC/LPV/r therapy and at periodic intervals during therapy.
Lipid disorders should be managed as clinically appropriate.

Excipients

ABC/3TC/LPV/r contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take the drug.

ABC/3TC/LPV/r 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

4.5 Interaction with other medicinal products and other forms of interaction

Medicine interactions

Anti-mycobaterials
Rifampicin:
Should not be co-administered with rifampicin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect.
Bedaquiline:
Co-administration of bedaquiline with strong CYP3A4 inhibitors like Lopinavir and ritonavir contained in the drug may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions .

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Bedaquiline must be used cautiously with the drug, only if the benefit of coadministration outweighs the risk.

Delamanid:

co-administration of delamanid with a strong inhibitor of CYP3A4 lopinavir/ritonavir contained in the drug 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.

Corticosteroids

Concomitant use of lopinavir/ritonavir as contained in the drug 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 the drug 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.

PDE5 inhibitors

Co-administration of the drug 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 ABC/3TC/LPV/r.

Co-administration of ABC/3TC/LPV/r. 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.

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HMG-CoA reductase inhibitors
Caution should be exercised if HIV protease inhibitors, including lopinavir / ritonavir contained in ABC/3TC/LPV/r., are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolised by the CYP3A4 pathway like atorvastatin, as this may increase the potential for serious reactions such as myopathy, including rhabdomyolysis.

Tipranavir
The concomitant administration of ABC/3TC/LPV/r. and tipranavir is not recommended due to significant decreases in lopinavir exposure.

4.6 Pregnancy and Lactation

Pregnancy

ABC/3TC/LPV/r 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

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.

Lactation:

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Studies have indicated that abacavir, lamivudine and lopinavir are excreted in breast milk. Therefore, nursing mothers should not breastfeed their children while on ABC/3TC/LPV/r therapy.

Fertility:

There are no data on fertility.

4.7 Effects on ability to drive and use machines

There are less frequent reports of visual impairment due to use of ABC/3TC/LPV/r . Patients need to be aware of how ABC/3TC/LPV/r affects them before engaging in potentially dangerous activities such as driving or operating machinery.

4.8 Undesirable effects

Table 2: Side effects reported from individual formulations of ABC/3TC/LPV/r

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**

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Infections and infestations			*Frequent*: upper respiratory tract infection, lower respiratory tract infection, skin infections including cellulitis, folliculitis and furuncle. *Less frequent:* otitis media, bronchitis, sinusitis, furunculosis, bacterial infection, viral infection,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**
			pharyngitis, flu syndrome, gastroenteritis, sialadenitis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)			*Less frequent:* skin benign neoplasm, cyst, neoplasm.

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Blood and lymphatic system disorders		*Less frequent:* neutropenia, anemia, thrombocytopenia, pure red cell aplasia.	*Frequent*: anemia, leucopenia, lymphadenopathy and neutropenia.
Immune system disorders			*Frequent*: hypersensitivity including urticaria and angioedema. *Less frequent:* immune reactivation syndrome.
Endocrine disorders			*Less frequent:* hypogonadism, Cushing syndrome,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir** **component**
			hypothyroidism.

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Metabolism and nutrition disorders	*Frequent*: anorexia.	*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, weight gain, weight loss.
Psychiatric disorders			*Frequent*: anxiety. *Less frequent:* abnormal dreams, agitation, anxiety, confusion, depression, emotional lability,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**

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			decreased libido, nervousness, abnormal thinking, apathy.
Nervous system disorders	*Frequent*: headache.	*Frequent*: headache. *Less frequent:* paraesthesia, peripheral neuropathy.	*Frequent*: headache (including migraine), neuropathy including (peripheral neuropathy), dizziness, insomnia. *Less frequent:* amnesia, ataxia, encephalopathy, facial paralysis, hypertonia, neuropathy, paraesthesia, peripheral neuritis, somnolence, tremor, taste loss, taste perversion, migraine, dyskinesia, cerebral infarct, convulsion, extrapyramidal

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir** **component**

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			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.
Vascular disorders			*Less frequent:* hypertension, thrombophlebitis, vasculitis, varicose vein, deep thrombophlebitis, vascular disorder, postural hypotension.
Respiratory, thoracic and			*Less frequent:* *d*yspnoea, rhinitis,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir** **component**

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mediastinal disorders			asthma, lung oedema, increased coughing.
Gastrointestinal disorders	*Frequent*: nausea, vomiting, diarrhoea.	*Frequent*: nausea, vomiting, upper abdominal pain, diarrhoea. *Less frequent:* pancreatitis, rises in serum amylase.	*Frequent*: diarrhoea, nausea, pancreatitis vomiting, gastrooesophageal reflux disease, gastroenteritis and colitis abdominal pain (upper and lower), abdominal distension, dyspepsia, haemorrhoids, flatulence. *Less frequent:* gastrointestinal haemorrhage including gastrointestinal ulcer, duodenitis, gastric ulcer, gastritis, mouth ulcerations, rectal haemorrhage,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**

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			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 fatty deposit, liver tenderness.
Skin and subcutaneous tissue disorders		*Frequent*: rash, alopecia	*Frequent*: rash including maculopapular rash, dermatitis/ rash including eczema and seborrheic dermatitis, night sweats, pruritus, alopecia, capillaritis, vasculitis. *Less frequent:* dry

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**

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			skin, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiform, alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, nail disorder, pruritis, seborrhoea, skin discolouration, skin 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,

System organ class	**Abacavir component**	**Lamivudine component**	**Lopinavir / ritonavir component**

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			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. *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.

Post-marketing data

Table 3: Post-marketing side effects reported from individual formulations of ABC/3TC/LPV/r

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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.	
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 multiform, Stevens-Johnson syndrome and	Stevens-Johnson Syndrome and erythema multiform.
System organ class	**Abacavir component**	**Lopinavir / ritonavir component**

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	toxic epidermal necrolysis.	
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.	

Clinical Trials Experience in Pediatric Subjects

Abacavir and lamivudine

The safety database to support abacavir and lamivudine once daily in pediatric 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 pediatric subjects receiving either once or twice daily dosing compared to adults.

Lopinavir and ritonavir

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

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications:

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https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of ABC/3TC/LPV/r
You may also report any suspected side effects (to Cipla Medpro (Pty) Ltd) by e-mail: 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

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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.

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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 harboring 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*.

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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 1-1,5 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.

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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

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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 2-4 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.

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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.

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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
ABC/3TC/LPV/r 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
ABC/3TC/LPV/r 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 – 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

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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.

5.3 Preclinical safety data

An increased incidence of malignant and non-malignant tumours occurred when abacavir 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.

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 and 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 and 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

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Ink S-1-8114 Black and 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 all medicines out of reach of children.

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

6.5 Nature and Content of container

Carton containing HDPE container of 120 capsules each 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. Marketing Authorization Holder

CIPLA LIMITED

8. Marketing Authorization Number

CTD 8910

9. Date of first authorization/renewal of the authorization

03/03/2023

10. Date of revision of the text

19/05/2025