Abacavir (as sulfate)/Lamivudine Tablets
600 mg/300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abacavir (as sulfate)/Lamivudine Tablets 600 mg/300 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Abacavir (as sulfate) USP equivalent to Abacavir	600 mg
Lamivudine USP	300 mg

Azo colouring agent sunset yellow (E110) – 0.18 mg/tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow colored, biconvex, film coated tablets debossed with "M 157" one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets, two nucleoside analogues, is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age.

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV infection.

Adults and adolescents
The recommended dose of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets in adults and adolescents is one tablet once daily.

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets should not be administered to adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets can be taken with or without food.

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets should not be prescribed for patients requiring dosage adjustments. Separate preparations of abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

Renal impairment: The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min.

Hepatic impairment: No data are available in patients with moderate hepatic impairment, therefore the use of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is not recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended. The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is contraindicated in patients with severe hepatic impairment.

Elderly: No pharmacokinetic data are currently available in patients over 65 years of age. Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Children: The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is not recommended for treatment of children less than 12 years of age as the necessary dose adjustment cannot be made.

4.3 Contraindications

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is contraindicated in patients with known hypersensitivity to the active substances or to any of the excipients. See BOXED INFORMATION ON ABACAVIR HYPERSENSITIVITY REACTIONS

Patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

The special warnings and precautions relevant to abacavir and lamivudine are included in this section.

There are no additional precautions and warnings relevant to the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets.

Hypersensitivity Reaction

In clinical studies approximately 5% of subjects receiving abacavir develop a hypersensitivity reaction. Some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. Based on the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity reactions. In populations similar to that enrolled in the PREDICT-1 study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B*5701 allele.

These results are consistent with those of prior retrospective studies.

As a consequence, before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available based on the treatment history and resistance testing.

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. It is noteworthy that among patients with a clinically suspected hypersensitivity reaction, a proportion did not carry HLA-B*5701. Therefore, even in the absence of HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Skin patch testing was used as a research tool for the PREDICT-1 study but has no utility in the clinical management of patients and therefore should not be used in the clinical setting.

• Clinical Description

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough, and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, **and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis**. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life threatening. These symptoms usually resolve upon discontinuation of abacavir.

• Clinical Management

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions **may occur at any time during therapy**. Patients should be monitored closely, especially during the first two months of treatment with abacavir, with consultation every two weeks.
Patients who are diagnosed with a hypersensitivity reaction whilst on therapy **MUST discontinue the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets immediately.**

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg, or any other medicinal product containing abacavir, MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets 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 medicinal products).

Special care is needed for those patients simultaneously starting treatment with the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is currently difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

• Management after an interruption of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets therapy

If therapy with the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets or any other medicinal product containing abacavir must not be restarted**.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir 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 this must be done in a setting where medical assistance is readily available.

• 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.
- Patients developing signs or symptoms possibly linked with a hypersensitivity reaction **MUST CONTACT their doctor IMMEDIATELY.**
- Patients who are hypersensitive to abacavir should be reminded that they must never take the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets or any other medicinal product containing abacavir again.
- In order to avoid restarting abacavir, patients who have experienced a hypersensitivity reaction should dispose of their remaining the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets in their possession in accordance with the local requirements, and ask their doctor or pharmacist for advice.
- Patients who have stopped the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Patients should be advised of the importance of taking the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets regularly.

- Each patient should be reminded to read the Package Leaflet included in the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets package.
- They should be reminded of the importance of removing the Alert Card included in the package, and keeping it with them at all times.

Lactic acidosis: Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis: Pancreatitis has been reported, but a causal relationship to lamivudine and abacavir is uncertain.

Triple nucleoside therapy: There have been reports of a high rate of virological failure, and of emergence of resistance at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil fumarate as a once daily regimen.

Liver disease: If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SPC.

The safety and efficacy of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets has not been established in patients with significant underlying liver disorders. The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is contraindicated in patients with severe hepatic impairment.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis (see Zeffix SPC).

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 according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

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. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Opportunistic infections: Patients should be advised that the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of HIV: Patients should be advised that current antiretroviral therapy, including the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets, 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: Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Excipients: The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets contains the azo colouring agent sunset yellow, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets contains abacavir and lamivudine, therefore any interactions identified for these individually are relevant to the fixed-dose combination Abacavir (as sulfate) 600 mg /

Lamivudine 300 mg tablets. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Abacavir and lamivudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Interactions relevant to abacavir

Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may via their action on UDP-glucuronyltransferases slightly decrease the plasma concentrations of abacavir.

The metabolism of abacavir is altered by concomitant consumption of ethanol resulting in an increase in AUC of abacavir of about 41%. These findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a 1 hour delay in t_{max}, but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. The induction of metabolizing enzymes cannot therefore be excluded. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

Interactions relevant to lamivudine

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. The possibility of interactions with other medicinal products administered concurrently with the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets should be considered, particularly when the main route of elimination is active renal secretion, especially via the cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. zidovudine and didanosine) are not metabolised by this mechanism and are unlikely to interact with lamivudine.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40% increase in lamivudine exposure, because of the trimethoprim component. However,

unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. The pharmacokinetics of trimethoprim or sulfamethoxazole are not affected. When concomitant administration with cotrimoxazole is warranted, patients should be monitored clinically. Co-administration of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets with high doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis should be avoided.

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

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is therefore not recommended to be used in combination with zalcitabine.

4.6 Pregnancy and lactation

The fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets is not recommended during pregnancy. The safety of abacavir and lamivudine in human pregnancy has not been established. Studies with abacavir and lamivudine in animals have shown reproductive toxicity.

It is recommended that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV. Lamivudine is excreted in human milk at similar concentrations to those found in serum. It is expected that abacavir will also be secreted into human milk, although this has not been confirmed. It is therefore recommended that mothers do not breast-feed their babies while receiving treatment with the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. The clinical status of the patient and the adverse event profile of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse reactions reported for the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets were consistent with the known safety profiles of abacavir and lamivudine when given as separate medicinal products. For many of these adverse reactions it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

Abacavir hypersensitivity

In clinical studies, approximately 5% of subjects receiving abacavir developed a hypersensitivity reaction. In clinical studies with abacavir 600 mg once daily the reported rate of hypersensitivity remained within the range recorded for abacavir 300 mg twice daily.

Some of these hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions. This reaction is characterised by the appearance of symptoms indicating multiorgan/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. These have been identified either from clinical studies or post marketing surveillance. Those reported **in at least 10% of patients** with a hypersensitivity reaction are in bold text.

Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain,** mouth ulceration
Respiratory tract	**Dyspnoea, cough,** sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests**, hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine Phosphokinase
Urology	Elevated creatinine, renal failure

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, 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 the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets regularly.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction was usually more severe than on initial presentation, and may include life-threatening hypotension and death. **Patients who develop this hypersensitivity reaction must discontinue the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets and must never be rechallenged with the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg, or any other medicinal product containing abacavir**.

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

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir 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 this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir.

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 the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicinal product 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 medicinal products containing abacavir should be permanently discontinued.

The adverse reactions considered at least possibly related to abacavir or lamivudine are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10,000 to < 1/1000), very rare (< 1/10,000).

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders		*Uncommon:* Neutropenia and anaemia (both occasionally severe), thrombocytopenia *Very rare:* Pure red cell aplasia
Immune system disorders	*Common:* hypersensitivity	
Metabolism and nutrition disorders	*Common:* anorexia	
Nervous system disorders	*Common:* headache	*Common:* Headache, insomnia. *Very rare:* Cases of peripheral neuropathy (or paraesthesia) have been reported
Respiratory, thoracic and mediastinal disorders		*Common:* Cough, nasal symptoms
Gastrointestinal disorders	*Common:* nausea, vomiting, diarrhoea *Rare:* pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain	*Common:* Nausea, vomiting, abdominal pain or cramps, diarrhoea *Rare:* Rises in serum amylase. Cases of pancreatitis have been reported
Hepatobiliary disorders		*Uncommon:* Transient rises in liver enzymes (AST, ALT), *Rare:* Hepatitis
Skin and subcutaneous tissue disorders	*Common:* rash (without systemic symptoms) *Very rare:* erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	*Common:* Rash, alopecia
Musculoskeletal and connective tissue disorders		*Common:* Arthralgia, muscle disorders *Rare:* Rhabdomyolysis
General disorders and Administration site conditions	*Common:* fever, lethargy, fatigue.	*Common:* fatigue, malaise, fever.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

4.9 Overdose

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

If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological Classification: 7.13 Antivirals.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors (NRTIs), ATC code: J05AR02.

Mechanism of action: Abacavir and lamivudine are NRTIs, and are potent selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Abacavir shows synergy *in vitro* in combination with amprenavir, nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, stavudine and lamivudine.

In-vitro resistance: HIV-1 resistance to lamivudine involves the development of a M184I or, more commonly, M184V amino acid change close to the active site of the viral RT. Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro*, requiring multiple mutations for a clinically relevant increase in EC_{50} over wild-type virus.

In vivo resistance (Therapy-naïve patients): The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy.

Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%) (see Table). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

Therapy	**Abacavir + fixed-dose combination (Lamivudine / Zidovudine 150 mg / 300 mg)**	**Abacavir + Lamivudine + NNRTI**	**Abacavir + Lamivudine + PI (or PI / Ritonavir)**	**Total**
Number of Subjects	282	1094	909	2285
Number of Virological Failures	43	90	158	306
Number of On-Therapy Genotypes	40 (100%)	51 (100%)[1]	141 (100%)	232 (100%)
K65R	0	1 (2%)	2 (1%)	3 (1%)
L74V	0	9 (18%)	3 (2%)	12 (5%)
Y115F	0	2 (4%)	0	2 (1%)
M184V/I	34 (85%)	22 (43%)	70 (50%)	126 (54%)
TAMs[2]	3 (8%)	2 (4%)	4 (3%)	9 (4%)

1. Includes three non-virological failures and four unconfirmed virological failures.
2. Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

In vivo resistance (Therapy experienced patients): The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy and confer high-level resistance to lamivudine. *In vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTIs should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTIs are available.

Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where ABC was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies) showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 ($p=0.015$) or 4 or more mutations at median Week 24 ($p\leq0.012$). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

Baseline Reverse Transcriptase Mutation	**Week 4 (n = 166)**		
	n	**Median Change vRNA (log_{10} c/mL)**	**Percent with <400 copies/mL vRNA**
None	15	-0.96	40%
M184V alone	75	-0.74	64%
Any one NRTI mutation	82	-0.72	65%
Any two NRTI associated mutations	22	-0.82	32%
Any three NRTI associated mutations	19	-0.30	5%
Four or more NRTI associated mutations	28	-0.07	11%

Phenotypic resistance and cross-resistance: Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple

TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. PIs or NNRTIs is unlikely.

Clinical experience

Therapy-naïve patients
The combination of abacavir and lamivudine as a once daily regimen is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients (CDC stage A). They were randomised to receive either abacavir (ABC) 600 mg once daily or 300 mg twice daily, in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA < 50 copies/ml at Week 48 ITT-Exposed Population		
Treatment regimen	**ABC once/day (N = 384)**	**ABC twice/day (N = 386)**
Virological response	**253/384 (66%)**	**261/386 (68%)**

Similar clinical success (point estimate for treatment difference: -1.7, 95% CI –8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load > 50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, there was a trend toward a higher rate of NRTI-associated mutations in the once daily versus the twice daily abacavir regimens. No firm conclusion could be drawn due to the limited data derived from this study. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

Therapy-experienced patients

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an

NNRTI for 48 weeks. Results indicate that the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (AAUCMB, - 1.65 $\log_{10}$ copies/ml versus -1.83 $\log_{10}$ copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets plus a PI or NNRTI for 48 weeks. Results indicate that the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

5.2 Pharmacokinetic properties

The fixed-dose combination tablet of abacavir/lamivudine (FDC) has been shown to be bioequivalent to lamivudine and abacavir administered separately. This was demonstrated in a single dose, 3-way crossover bioequivalence study of FDC (fasted) versus 2 x 300 mg abacavir tablets plus 2 x 150 mg lamivudine tablets (fasted) versus FDC administered with a high fat meal, in healthy volunteers (n = 30). In the fasted state there was no significant difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component. There was also no clinically significant food effect observed between administration of FDC in the fasted or fed state. These results indicate that FDC can be taken with or without food. The pharmacokinetic properties of lamivudine and abacavir are described below.

Absorption: Abacavir and lamivudine are rapidly and well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83% and 80-85% respectively. The mean time to maximal serum concentrations (t_{max}) is about 1.5 hours and 1.0 hour for abacavir and lamivudine, respectively. Following a single dose of 600 mg of abacavir, the mean (CV) C_{max} is 4.26 μg/ml (28%) and the mean (CV) AUC_{∞} is 11.95 μg.h/ml (21%). Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2.04 μg/ml (26%) and the mean (CV) AUC_{24} is 8.87 μg.h/ml (21%).

Distribution:
Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0.8 and 1.3 l/kg respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~49%) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding *in vitro* (< 36%). This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of abacavir of 0.08 μg/ml or 0.26 μM when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism: Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine.

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%).

Elimination: The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces.

The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, predominantly by renal clearance (> 70%) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance < 50 ml/min.

Intracellular pharmacokinetics

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the

geometric mean abacavir plasma half-life in this study of 2.6 hours. In a crossover study in 27 HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32 %, $C_{max24,ss}$ + 99 % and C_{trough} + 18 %) compared to the 300 mg twice daily regimen. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16-19 hours, compared to the plasma lamivudine half-life of 5-7 hours. In a crossover study in 60 healthy volunteers, intracellular lamivudine-TP pharmacokinetic parameters were similar ($AUC_{24,ss}$ and $C_{max24,ss}$) or lower (C_{trough} – 24 %) for the lamivudine 300 mg once daily regimen compared to the lamivudine 150 mg twice daily regimen. Overall, these data support the use of lamivudine 300 mg and abacavir 600 mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021- See Clinical experience).

Special populations

Hepatically impaired: There are no data available on the use of the fixed-dose combination Abacavir (as sulfate) 600 mg / Lamivudine 300 mg tablets in hepatically impaired patients. Pharmacokinetic data has been obtained for abacavir and lamivudine alone.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dosage reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure.

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

Renally impaired: Pharmacokinetic data have been obtained for lamivudine and abacavir alone. Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction is required for patients with creatinine clearance of < 50 ml/min.

Elderly: No pharmacokinetic data are available in patients over 65 years of age.

5.3 Preclinical safety data

With the exception of a negative *in vivo* rat micronucleus test, there are no data available on the effects of the combination of abacavir and lamivudine in animals.

Mutagenicity and carcinogenicity

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues. The results of an *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies at doses that gave plasma concentrations up to 30-40 times higher than clinical plasma concentrations. Abacavir has a weak potential to cause chromosomal damage both *in vitro* and *in vivo* at high tested concentrations.

The carcinogenic potential of a combination of abacavir and lamivudine has not been tested. In longterm oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Repeat-dose toxicity

In toxicology studies abacavir was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in man.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Reproductive toxicology

In reproductive toxicity studies in animals, lamivudine and abacavir were shown to cross the placenta.

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Abacavir demonstrated toxicity to the developing embryo and foetus in rats, but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose, Colloidal silicon dioxide, Magnesium stearate, Sodium starch glycolate, Film coat {Hypromellose, Titanium dioxide, Polyethylene glycol 400, Iron oxide yellow, Polysorbate 80 and Sunset yellow aluminium lake}.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Round wide mouth white high density polyethylene bottle with a white opaque polypropylene screw closure with aluminium induction sealing wad, containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. SUPPLIER

Mylan Laboratories Limited
Plot No. 564/A/22,
Road No.92, Jubilee Hills
Hyderabad - 500034,
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Manufacturer:
Mylan Laboratories Limited (FDF Unit – 1)
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

8. DATE OF REVISION OF THE TEXT

December 2015.

References
1. SmPC of Kivexa Tablets (GSK, UK)