Abacavir (as sulfate) / Lamivudine 120 mg / 60 mg
Dispersible Tablets

1. NAME OF THE MEDICINAL PRODUCT

Abacavir (as sulfate) / Lamivudine 120 mg / 60 mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:

Abacavir (as sulfate) USP equivalent to Abacavir	120 mg
Lamivudine USP	60 mg

This medicinal product contains aspartame (source of phenylalanine).
May be harmful for people with phenylketonuria.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet.

A white to off-white, round, biconvex tablet with a criss-cross score on both sides of the tablet and debossed with "M" on the top left of the score over "A" on the bottom left of the score and "L" on the bottom right of the score on one side of the tablet.

The tablet can be divided into four equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children (see also "*Special warnings and special precautions for use*" concerning Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible Tablets use and HLA-B*5701 screening).

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).
This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

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

Children 6 weeks of age and above:

Number of tablets by weight band to be taken once daily (approximately 24 hours apart)

Number of tablets by weight band (once daily)				
3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg
1	1.5	2	2.5	3

The breaking of the tablets in halves allows most of the required posology adjustments. The use of one-fourth tablets may also be useful to adjust the posology prescribed by the physician.

Children who can reliably swallow tablets should swallow the tablet whole.
For very young children who cannot swallow the tablets whole, each tablet should be dispersed in 10 ml of drinking water prior to administration.

Children weighing 25 kg or more, adolescents and adults:

For these patient groups other formulations with higher amounts of the active substances are available. Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets can be taken with or without food.

Dose adjustments

Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments. Separate formulations of abacavir and 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 product information of the individual medicinal product.

Renal impairment: Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min, as appropriate dose adjustments are not possible. For such patients, separate formulations of abacavir and lamivudine should be used.

Hepatic impairment: No data are available in patients with moderate hepatic impairment, therefore the use of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is not recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required. Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is contraindicated in patients with severe hepatic impairment.

4.3 Contraindications

Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is contraindicated in patients

- with known hypersensitivity to any of the active substances or to any of the excipients (for abacavir hypersensitivity, see *"Special warnings and special precautions for use" and "Undesirable effects"*)
- with severe hepatic impairment.

4.4 Special warnings and special precautions for use

Abacavir hypersensitivity reaction

In clinical studies approximately 5% of subjects receiving abacavir developed 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. In a prospective study, 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 this study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have this allele.

These results are consistent with those of prior retrospective studies.

As a consequence, screening for carriage of the HLA-B*5701 allele is recommended in any HIV-infected patient without prior exposure to abacavir. Overall frequencies of hypersensitivity reactions have been reported to vary across different racial groups (e.g. lower frequency in African Americans and black Africans). Nevertheless, screening for HLA-B*5701 should be performed in any patient irrespective of race. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see "*Management after an interruption of abacavir therapy*"). Abacavir should not be used in patients known to carry the HLA-B*5701 allele. Only in the rare case where no other therapeutic option is available based on the treatment history, drug tolerability and resistance testing, the use of abacavir might be considered. However, such patients must be very closely monitored for signs and symptoms of a hypersensitivity reaction.

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

Skin patch testing is not a tool for prospectively evaluating abacavir tolerability in abacavir-naïve patients. It has not been thoroughly evaluated for use in routine clinical management of patients, and should not be used as a substitute for genotyping for HLA-B*5701.

<u>Clinical Description</u>

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 Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets immediately.

Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets or any other abacavir-containing product 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, Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible 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 medications).

Special care is needed for those patients simultaneously starting treatment with abacavir and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

Management after an interruption of abacavir therapy

If therapy with abacavir 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, 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.

Since on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for its signs and symptoms.

Screening for carriage of the HLA B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

Essential patient information

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

- Patients' caregivers must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death.
- Caregivers of patients developing signs or symptoms possibly linked to a hypersensitivity reaction MUST CONTACT the patient's doctor IMMEDIATELY.
- Patients who are hypersensitive to abacavir (and their caregivers) should be reminded that they must never take Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets or any other medicinal product containing abacavir.
- In order to avoid restarting abacavir, the caregivers of patients who have experienced a hypersensitivity reaction should be asked to return the remaining abacavir-containing tablets to the pharmacy.
- Patients who have stopped Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each patient (caregiver) should be reminded to read the Package Leaflet included in the Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with use of nucleoside reverse transcriptase inhibitors. Several other agents of this class are known to cause lactic acidosis. Whereas this has not clearly been shown for the combination of abacavir and lamivudine, an association cannot be excluded. Lactic acidosis may occur after a few to several months of nucleoside reverse transcriptase inhibitor (NRTI) treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity.

Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Mitochondrial dysfunction

NRTIs 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 postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). 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.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for abacavir and lamivudine as causative agents is weak; indeed switching from a thymidine analogue to abacavir has been shown to increase limb fat in patients with lipoatrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir or lamivudine treatment is uncertain.

Myocardial infarction

Observational studies in adults 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 Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible Tablets, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Combination therapy with abacavir

Abacavir should only be used in combination with zidovudine in the treatment of antiretroviral naïve patients in situations when a regimen based on a protease inhibitor (PI) or NNRTI cannot be used. Abacavir and lamivudine should not be used as part of a triple combination regimen including tenofovir.

Liver disease

Caution should be exercised when administering lamivudine to any patient with hepatitis B co-infection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. Periodic monitoring of liver function tests and markers of HBV replication is recommended for at least four months if lamivudine is discontinued in HBV co-infected patients.
The safety and efficacy of abacavir has not been established in patients with significant underlying liver disorders. Clinical safety data with abacavir in patients with mild hepatic impairment is very limited and pharmacokinetic data show substantial variability of drug exposure in this population. Therefore, close safety monitoring is required.

No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these patients. Therefore, the use of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets in patients with moderate hepatic impairment is not recommended unless judged necessary and requires close monitoring of these patients. For patients with severe hepatic impairment, Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets is contraindicated.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased risk of liver function abnormalities as well as severe and potentially fatal hepatic adverse events. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see also precautionary measures described above). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Immune Reactivation Syndrome

In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, *Pneumocystis pneumonia*) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be 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 (adult) patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving abacavir or any other antiretroviral therapy 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

Treatment with Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Excipients

Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets contains aspartame, which is a source of phenylalanine. It may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicinal products involving abacavir are low. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine does not inhibit the cytochrome P450 isoform CYP3A.

Interactions relevant to abacavir

Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may, via their effects on UDP-glucuronyltransferases, decrease the plasma concentrations of abacavir. The magnitude of any such effects, as well as their possible clinical consequences, are unknown.

Ethanol: The metabolism of abacavir is altered by concomitant intake 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.

Methadone**:** Abacavir co-administration increased the mean methadone systemic clearance by 22%, possibly due to induction of drug metabolising enzymes. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms and methadone doses should be adjusted accordingly.

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

Lopinavir and ritonavir: In a pharmacokinetic study, coadministration of 600 mg abacavir once daily with lopinavir/ritonavir 400/100 mg twice daily led to a 32% decrease in abacavir plasma AUC. The clinical relevance of this is unknown.

***Tipranavir and ritonavir*:** Co-administration of abacavir and tipranavir + ritonavir decreased the plasma AUC of abacavir by approximately 40%. The clinical relevance is unknown.

***Ribavirin*:** Though evidence is conflicting, co-administration of abacavir and ribavirin has been associated with a lower response rate to ribavirin-containing hepatitis C treatment. If possible, abacavir should be substituted by another NRTI (e.g. tenofovir) when co-treating with ribavirin.

Interactions relevant to Lamivudine

Because of overlapping resistance and lack of additive antiretroviral effects, lamivudine should not be co-administered with emtricitabine.

Co-administration with trimethoprim / sulfamethoxazole results in a 40% increase in lamivudine area under the concentration curve because of the trimethoprim component. Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

4.6 Pregnancy and Lactation

Pregnancy

No increased risk of birth defects has been reported for abacavir or lamivudine (www.apregistry.com). However, risks to the fetus cannot be ruled out. Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets should not be initiated during pregnancy due to the risk of a hypersensitivity reaction to abacavir. If a patient becomes pregnant during treatment with Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets, however, Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets therapy may be continued if the benefit is considered to outweigh the risk.

Breastfeeding

Lamivudine, and probably also abacavir, are excreted into the breast milk of lactating mothers. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter.
Preferred options may vary depending on the local circumstances.

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.

Nevertheless, the clinical status of the patient and the adverse reaction profile of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Abacavir hypersensitivity

In clinical studies, approximately 5% of subjects receiving abacavir developed a hypersensitivity reaction.

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 multi-organ/body-system involvement.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

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

Rash (81% vs 67% respectively) and **gastrointestinal manifestations** (70% vs 54% respectively) were **more frequently** reported in **children** compared to adults**.**

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 always be considered for patients that have recently initiated abacavir treatment and that present 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. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It has been suggested that intermittent therapy may increase the risk of developing clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible 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. Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets and must never be rechallenged with Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets, or any other medicinal product containing abacavir.

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.

For many of the other adverse reactions reported, it is unclear whether they are related to abacavir and/or lamivudine, to other medicinal products used in the management of HIV infection, or are a result of the disease process.

Many of those listed 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 a hypersensitivity reaction. If abacavir has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart therapy with an abacavir-containing product, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for signs and symptoms. 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 following convention has been used for the classification of adverse reactions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

Metabolism and nutrition disorders
Common: anorexia
Not known: lipodystrophy, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia, lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis.

Musculoskeletal and connective tissue disorders:
Common: arthralgia
Rare: rhabdomyolysis
Not known: osteonecrosis.

Nervous system disorders
Common: headache
Very rare: Peripheral neuropathy.

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea
Rare: pancreatitis.

Skin and subcutaneous tissue disorders
Common: rash, alopecia
Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

General disorders and administration site conditions
Common: fever, lethargy, fatigue
Not known: immune reconstitution syndrome.

Blood and lymphatic disorders
Uncommon: Neutropenia and anaemia, thrombocytopenia
Very rare: Pure red cell aplasia.

Hepatobiliary disorders
Rare: hepatitis.

Laboratory abnormalities
Uncommon: Transient rises in liver enzymes

4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir (i.e. two to three times the normal adult dose) have been administered to adult patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. The rate of removal of abacavir by haemodialysis is low.

No specific symptoms or signs have been identified following acute overdose with lamivudine apart from those listed as undesirable effects. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors (NRTIs), Antivirals for treatment of HIV infections, combinations, ATC code: J05AR02

Mechanism of action

Abacavir and lamivudine are NRTIs. Both agents are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP). Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir). They are competitive inhibitors of the reverse transcriptase (RT) of both HIV-1 and HIV-2. Abacavir and lamivudine show significantly less affinity for host cell DNA polymerases.

Clinical efficacy

Adults

In antiretroviral therapy-naïve adult patients treated with abacavir 300 mg twice daily, together with lamivudine and efavirenz, the proportion of patients with plasma HIV-1 RNA $\leq$50 copies/ml by Week 48 was 70%, by intention-to-treat analysis. Though the clinical benefit of abacavir has otherwise mainly been demonstrated in combination with lamivudine and zidovudine, this triple nucleoside regimen is no longer recommended as a preferred treatment option, due to inferior efficacy compared to NNRTI- or PI-containing regimens.

Children

Among 45 antiretroviral therapy-naïve children aged 3 months to 16 years receiving abacavir/lamivudine in combination with nelfinavir (except 6 patients who received only the dual NRTI combination) 56% had viral load <50 copies after 48 weeks of treatment.

Resistance

In the pivotal clinical trials, the most common mutation emerging in patients failing on abacavir containing regimens (also including lamivudine) was M184V/I. Other key mutations appearing, though more rarely, include L74V and K65R. When occurring together with M184V/I, either of these mutations substantially reduce the activity of abacavir. The presence of M184V with K65R gives rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. A further mutation selected for and

reducing the activity of abacavir is Y115F. Though TAMs (M41L, D67N/G, K70R, L210W, T215F/Y, K219E/Q/N/R) are generally not selected for when failing on abacavir-containing regimens in the absence of thymidine analogues, the presence of two or more together with M184V will substantially reduce the activity of abacavir. In addition, the 69 insertion complex or the Q151M mutation cause a high level of resistance to abacavir.

When combination antiretroviral therapy comprising lamivudine fails virologically, the M184V mutation will be selected for at an early stage (particularly if the regimen does not contain a boosted PI). M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). 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. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

5.2 Pharmacokinetic properties

Abacavir

Absorption

Abacavir is rapidly absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%.

Following single dose administration of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets in healthy volunteers, the mean (± SD) abacavir C_{max} value was 8451.7355 (±2362.3239) ng/ml, and the corresponding value for AUC was 20101.6699 (± 4374.9209) ng.h/ml. The mean (± SD) abacavir t_{max} value was 0.500 (0.167 – 2.000) hours.

Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets can be taken with or without food.

Distribution

Following intravenous administration, the apparent volume of distribution was about 0.8 l/kg. Plasma protein binding to human plasma proteins at therapeutic concentrations is ~49%. Studies in HIV-infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%.

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.

Elimination

The mean plasma 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.

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. Overall, these data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients.

Special populations

Hepatic impairment: 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 in the abacavir AUC, and 1.58-fold in the elimination half-life. No recommendation on dosage adjustments can be given for this patient population due to the substantial variability of abacavir exposure. No pharmacokinetic data are available for patients with moderate to severe hepatic impairment.

Renal impairment: The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment.

Children: The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. Dosing according to weight bands is recommended for abacavir tablets based primarily on pharmacokinetic modelling. Higher exposures of abacavir can occur in some paediatric patients since accurate dosing cannot be achieved with this formulation. Therefore, children should be closely monitored for abacavir toxicities.
There are insufficient data to recommend the use of abacavir in infants less than six weeks old.

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

Lamivudine

Absorption

Lamivudine is rapidly absorbed following oral administration. Bioavailability is between 80 and 85% and is not altered by food intake.

Following single dose of administration of Abacavir (as sulfate) 120 mg / Lamivudine 60 mg dispersible tablets in healthy volunteers, mean (± SD) lamivudine C_{max} value was 2909.7585 (± 854.2833) ng/ml and the corresponding value for AUC was 14285.4980 (± 3588.1734) ng.h/ml. The mean (± SD) lamivudine t_{max} values was 1.250 (0.500 – 3.000) hours.

Distribution

Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 l/kg. Lamivudine displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*).

Metabolism

Metabolism of lamivudine is a minor route of elimination.

Elimination

The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system.

Special populations

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

Renal impairment: Studies in patients with renal impairment show that lamivudine elimination decreases with increasing degrees of renal dysfunction. Therefore, dose adjustment may be necessary. If so, separate formulations of abacavir, lamivudine and zidovudine must be used.

Children: In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 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. 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 long-term 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 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. 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, Croscarmellose Sodium, Magnesium Stearate, Aspartame, Strawberry Flavor.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 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

HDPE bottle (pack of 30 tablets) (marketable pack) comprises of Round wide mouth white High Density Polyethylene bottle with white opaque polypropylene screw cap. Absorbent cotton: Well bleached cotton fiber, soft, hair like white filaments.

6.6 Instructions for use and handling and disposal

No special requirements.

References

The main reference source for this text is the European SPC for Ziagen, Kivexa and Epivir, available at: http://www.ema.europa.eu/humandocs/Humans/EPAR/ziagen/ziagen.htm., http://www.ema.europa.eu/humandocs/Humans/EPAR/kivexa/kivexa.htm and http://www.ema.europa.eu/humandocs/Humans/EPAR/epivir/epivir.htm, respectively, and the US prescribing information for Ziagen, available at: us.gsk.com/products/assets/us_ziagen.pdf

Further references relevant to sections of the SmPC include:

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