PUBLIC ASSESSMENT REPORT

Abacavir Sulfate Oral Solution

International Nonproprietary Name (INN): **Abacavir**

Abstract

Abacavir Sulfate Oral Solution, supplied by Aurobindo Pharma, Ltd., Unit III, Survey No. 313 & 314, Bachupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India 500-072, was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Abacavir Sulfate Oral Solution is safe and effective for use as recommended in the submitted labeling. The USFDA was unable to grant final approval to this ANDA at the time of review due to existing patent protection. Therefore, the ANDA was **tentatively approved** on June 27, 2006. This determination is based upon information available to the agency (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product.

Abacavir Sulfate Oral Solution, on the basis of USFDA **tentative approval**, was placed on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification Programme list with the note "USFDA" are added to the list based on the scientific assessment and inspections conducted by the USFDA. Product listing as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of the product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

Abacavir Sulfate Oral Solution is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in combination with other antiretroviral agents. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC), which is Part 4 of this Public Assessment Report.

The demonstration of the benefit of Abacavir Sulfate Oral Solution is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy.

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.

The active pharmaceutical ingredient (API) of Abacavir Sulfate Oral Solution is the nucleoside reverse transcriptase inhibitor abacavir, a documented active substance for the treatment of HIV/AIDS in combination with other products. Current HIV treatment guidelines include abacavir in alternative non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) based treatment regimens for the initial treatment of HIV. When used as part of a recommended combination treatment regimen, abacavir is a potent NRTI.

Initial studies found that the combination of abacavir, lamivudine, and tenofovir resulted in poor efficacy and a high rate of virologic non-response. Therefore, this combination is not recommended as a triple NRTI regimen.

The most common adverse reactions reported with abacavir include nausea and vomiting, malaise, loss of appetite/anorexia, headache, and insomnia or other sleep disorders. Other adverse reactions that have been reported were pancreatitis and increased GGT. Abacavir is associated with a hypersensitivity reaction that occurs in approximately 5-10% of patients. This hypersensitivity reaction is associated with the HLA-B*5701 genetic marker, as well as the HLA-DR7 and HLA-DQ3 markers. In studies to date individuals who test positively for these markers appear to be more likely to develop a serious and potentially life-threatening hypersensitivity reaction characterized by fever, skin rash, fatigue, gastrointestinal symptoms, and, sometimes, respiratory symptoms. When a hypersensitivity reaction cannot be ruled out, abacavir treatment must be permanently discontinued and should never be used again in the same patient.

All Accepted Presentations

STATUS	INN	Strength	Form	Route of Administration	Packaging	Package Size
USFDA Tentative Approval	Abacavir	20 mg/mL	Solution	Oral	Bottle	240 mL

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Abacavir Sulfate Oral Solution

Read all of this leaflet carefully before you take this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider, or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

WARNING
Serious allergic reactions to abacavir are possible. Individuals taking abacavir may have a serious allergic reaction (known as a hypersensitivity reaction) that can cause death. Abacavir is also contained in other medicines called Ziagen® (abacavir sulfate), Epzicom™ (abacavir sulfate and lamivudine), and Trizivir® (abacavir sulfate, lamivudine, and zidovudine).

If you have a symptom from *any two or more* of the five symptom groups below, **STOP** taking Abacavir Sulfate Oral Solution and call your doctor or health care provider immediately.

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

Your pharmacist will give you a Warning Card. A list of these symptoms is on that card. Carry this Warning Card with you.

If you stop taking Abacavir Sulfate Oral Solution because of an allergic reaction, **NEVER** take Abacavir Sulfate Oral Solution or any abacavir-containing medicine again (Ziagen®, Epzicom™, or Trizivir®). If you take abacavir sulfate in any form or any abacavir-containing medicine again after you have had an allergic reaction, you may get life-threatening symptoms WITHIN HOURS that may include very low blood pressure or death.

If you stop taking Abacavir Sulfate Oral Solution for any reason other than allergy, even for a few days, **DO NOT START TAKING AGAIN** until you talk with your doctor. Taking abacavir after stopping it for any reason can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to abacavir before. If your doctor or any doctor tells you that you can take abacavir sulfate again, start taking it when you are near medical help or people who can call a doctor or take you to a doctor if needed.

In this leaflet:

1. WHAT ABACAVIR SULFATE ORAL SOLUTION IS AND WHAT IT IS USED FOR

Abacavir Sulfate Oral Solution is a prescription medicine used to treat HIV infection. Abacavir is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Abacavir Sulfate Oral Solution is always used with other anti-HIV medicines. When used in combination with these other medicines, abacavir helps lower the amount of HIV found in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Abacavir Sulfate does not cure HIV infection or AIDS. It is not known if Abacavir Sulfate will help you live longer or have fewer of the medical problems that people can get with HIV or AIDS. It is very important that you see your doctor or healthcare professional regularly while you are taking Abacavir Sulfate Oral Solution.

Abacavir Sulfate Oral Solution does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. You must continue to take all necessary precautions.

2. BEFORE YOU TAKE ABACAVIR SULFATE ORAL SOLUTION

Do not take Abacavir Sulfate Oral Solution if:

- you are allergic (hypersensitive) to abacavir sulfate or any of the other ingredients of Abacavir Sulfate Oral Solution (see Section 6, What Abacavir Sulfate Oral Solution Contains)
- have any sort of liver disease or a liver that is not functioning properly

Take special care with Abacavir Sulfate Oral Solution

Before using this medicine, you should tell your doctor or healthcare provider if you:

- Have been tested and know whether or not you have a particular gene variation called HLA-B*5701
- Are pregnant or planning to become pregnant. It is not known if Abacavir Sulfate will harm your unborn child. You and your doctor will need to decide if abacavir sulfate is right for you.
- Are breastfeeding. It is not known if Abacavir Sulfate can be passed to your baby in your breast milk and whether it could harm your baby. In general, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.
- Have liver problems or liver disease (such as hepatitis)
- Have heart problems, smoke, or suffer from diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes

The most common adverse reactions reported by people taking Abacavir Sulfate include nausea and vomiting, lack of energy, loss of appetite, headache, and insomnia or other sleep disorders.

People taking Abacavir Sulfate may have a serious allergic reaction (hypersensitivity reaction) that can cause death. Your risk of this reaction is much higher if you have a gene variation called HLA-B*5701 than if you do not. Your doctor or healthcare provider can determine with a blood test if you have this gene variation. If you get a symptom from 2 or more of the following groups of symptoms while taking Abacavir Sulfate, call your doctor, healthcare provider, or pharmacist immediately to determine if you should stop taking Abacavir Sulfate. You should also receive this list on a Warning Card given to you by your doctor, healthcare provider, or pharmacist at the time you receive Abacavir Sulfate Oral Solution. If you do not receive this card, ask for it.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, stomach pain
Group 4	Extremely tired, ache all over, "just don't feel well"
Group 5	Shortness of breath, cough, sore throat

If you stop taking Abacavir Sulfate Oral Solution because of an allergic reaction, **never again** take Abacavir Sulfate in any form or any other abacavir-containing medicine (including Epzicom™ or Trizivir®) again. *If you take Abacavir Sulfate Oral Solution or Abacavir Sulfate in any other form (such as tablets or abacavir included in other combination medicines) after you have had an allergic reaction, you may develop life-threatening symptoms within hours that may include very low blood pressure or death*.

If you are not allergic to Abacavir Sulfate but stop taking either Abacavir Sulfate Oral Solution or Abacavir Sulfate in any other form, even for a few days, talk with your doctor or healthcare provider before starting abacavir again. Taking Abacavir Sulfate again after stopping it can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take abacavir again, start taking it when you are near or have access to medical help or people who can call a doctor if you need one.

Some HIV medicines, including Abacavir Sulfate, can cause a rare but serious condition called lactic acidosis. Nausea and tiredness that do not improve may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.

You must take Abacavir Sulfate Oral Solution every day. Abacavir Sulfate helps to control your condition but is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor or healthcare provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines
Tell your doctor, healthcare provider, or pharmacist about any other medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. In

particular, you must tell your doctor, healthcare provider, or pharmacist if you take methadone or either of the anti-HIV medicines Epzicom™ or Trizivir® (both of which contain abacavir).

Taking Abacavir Sulfate Oral Solution with food and drink
Abacavir Sulfate Oral Solution can be taken with or without food.

Pregnancy and breastfeeding
Abacavir Sulfate is not recommended during pregnancy. In animal studies it was shown that Abacavir Sulfate can cross the placenta to the fetus, but Abacavir Sulfate's capacity to harm an unborn child could not be established from studies in animals.

There is no information available on the safety of Abacavir Sulfate when administered to babies less than three months old. It is therefore recommended that mothers do not breastfeed their babies while receiving treatment with abacavir. In general, it is recommended that HIV-infected women do not breastfeed under any circumstances in order to avoid transmission of HIV.

Driving and using machines
No studies on the effects of Abacavir Sulfate on the ability to drive or operate machines have been performed.

3. HOW TO TAKE ABACAVIR SULFATE ORAL SOLUTION

Always take Abacavir Sulfate Oral Solution exactly as your doctor or healthcare provider tells you to. If you are administering Abacavir Sulfate Oral Solution to your child, administer it exactly as your doctor or healthcare provider tells you to.

Check with your doctor, healthcare provider, or pharmacist if you have questions or need further instructions.

Abacavir Sulfate Oral Solution can be taken with or without food.

Adults: The recommended oral dose of Abacavir Sulfate for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral (anti-HIV) medicines.

Adolescents and Children: The recommended oral dose of Abacavir Sulfate for adolescents and children 3 months up to 16 years of age is 8 milligrams per kilogram of body weight, given twice daily up to a maximum of 300 mg twice daily, in combination with other antiretroviral (anti-HIV) medicines.

Your doctor or healthcare provider will advise you as to the correct dose to take or to administer to your child. If you are unclear about dose amount or schedule of dosing, ask for help.

If you take more Abacavir Sulfate Oral Solution than you should
Very little is known about the effects of Abacavir Sulfate overdose. If you take too much you should call your doctor, healthcare provider, pharmacist, or poison control center immediately.

If you forget to take Abacavir Sulfate Oral Solution
Try not to miss a dose. If you miss a dose, take that dose as soon as possible, but do not double the next regular dose.

If you stop taking Abacavir Sulfate Oral Solution
Do not stop taking Abacavir Sulfate Oral Solution unless you experience serious side effects or your doctor or healthcare provider tells you to stop. This is important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you stop Abacavir Sulfate Oral Solution because of an allergic reaction, do *not* resume taking Abacavir Sulfate Oral Solution or any other abacavir-containing medicine again. If you are not allergic to Abacavir Sulfate but stop taking either Abacavir Sulfate Oral Solution or Abacavir Sulfate in any other form for even a few days, talk with your doctor or healthcare provider before starting Abacavir Sulfate again (see above, "Take special care with Abacavir Sulfate Oral Solution").

4. POSSIBLE SIDE EFFECTS

Like all medicines, Abacavir Sulfate Oral Solution can cause side effects, although not everybody gets them. The most common side effects when taking Abacavir Sulfate (between 1 and 10 patients in 100) are loss of appetite, headache, nausea, vomiting, diarrhea, rash, fever, lack of energy, and tiredness.

Hypersensitivity reactions (allergic reactions) occur in about 5% of patients taking Abacavir Sulfate, usually within the first 6 weeks of treatment. Some of these cases can be fatal. The risk of hypersensitivity is higher in patients who have the HLA-B*5701 gene. Your doctor can order a blood test that will tell if you have this genetic marker. Symptoms of hypersensitivity almost always include fever or rash, but also very commonly include nausea, vomiting, diarrhea, abdominal pain, difficulty breathing, cough, fever, lethargy, headache, muscle pain, and also signs of liver damage revealed through blood tests your doctor or healthcare provider can order if indicated.

Patients treated with Abacavir Sulfate in any form should receive a card detailing these symptoms. If you experience or believe you experience any of the above noted symptoms, contact your doctor or healthcare provider immediately.

Abacavir Sulfate in any form should not be used in patients with severe liver disease or who may be hypersensitive (allergic) to Abacavir Sulfate or any of the other ingredients.

As with other anti-HIV medicines, patients taking Abacavir Sulfate in any form may be at risk of changes in the distribution of body fat (called lipodystrophy), death of bone tissue (called osteonecrosis), or immune reactivation syndrome (symptoms of infection caused by the recovering immune system). Patients who have problems with their liver (including hepatitis B or C infection) may be at an elevated risk of liver damage when taking Abacavir Sulfate in any form. As with all other NRTIs, Abacavir Sulfate may also cause lactic acidosis, a build-up of lactic acid in the body.

In the babies of mothers taking Abacavir Sulfate during pregnancy, damage to the energy-producing components inside human cells (known as "mitochondrial dysfunction") can occur.

If you experience, or believe you are experiencing, any of the side effects discussed above, contact your doctor or healthcare provider immediately.

5. HOW TO STORE ABACAVIR SULFATE ORAL SOLUTION

- Keep out of the reach and sight of children.
- Store at room temperature, 68° to 77°F (20° to 25°C). Do not store above 30°C (86°F). May be refrigerated but do not freeze. Store in the original container.
- Do not use Abacavir Sulfate Oral Solution after the expiry date which is printed on the bottle, label, and carton. The expiry date refers to the last day of that month.
- Do not use Abacavir Sulfate Oral Solution if there is any sign that the packaging has been opened or tampered with, or if you notice any visible signs of deterioration such as clumping or color changes of the solution.
- Medicines should not be disposed of via wastewater or household waste. Return any unused portion to your pharmacist.

6. FURTHER INFORMATION

What Abacavir Sulfate Oral Solution contains
The active ingredient of Abacavir Sulfate Oral Solution is abacavir sulfate. The other ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film made of hypromellose, polysorbate 80, iron oxide yellow, titanium dioxide, and triacetin.

What Abacavir Sulfate Oral Solution looks like and contents of the packaging
Abacavir Sulfate Oral Solution is a clear to opalescent, yellowish, strawberry-banana flavored liquid packaged in 240 mL bottles.

For further information about this medicinal product, contact the supplier: Aurobindo Pharma, Ltd., Unit III, Survey No. 313 & 314, Bachupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India 500-072.

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abacavir Sulfate Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Abacavir Sulfate Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL).
For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Abacavir Sulfate Oral Solution is a clear to opalescent, yellowish, strawberry-banana flavored liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir Sulfate Oral Solution is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

The demonstration of the benefit of abacavir is mainly based on results of studies performed with a twice-daily regimen, in treatment-naïve adult patients on combination therapy (see section 5.1).

Before initiating treatment with abacavir, screening for the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of age or 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 (see section 4.4 and 4.8).

4.2 Posology and method of administration

Abacavir Sulfate Oral Solution should be prescribed by physicians or healthcare providers experienced in the management of HIV infection.

Abacavir Sulfate Oral Solution can be taken with or without food.

Adults and adolescents (≥ 16 years of age and/or ≥ 35 kg): 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily (see sections 4.4 and 5.1).

Patients < 16 years of age and weighing ≥ 35 kg: the recommended dose is 300 mg twice daily (the adult maximum daily dose).

Children weighing between 5-35 kg: Dosing according to weight is recommended. The recommended dose of abacavir in any form (tablets, pediatric scored tablets, oral solution) for

pediatric and adolescent patients 3 months to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily).

For children who can swallow tablets, 60 mg scored tablets are recommended. See table below.

Abacavir Dosage Recommendations for Children Weighing Between 5-35 kg (60 mg tablets)

Weight (kg)	*AM Dose*	*PM Dose*	*Total Daily Dose*
5	½ tablet (30 mg)	1 tablet (60 mg)	90 mg
6 - < 9	1 tablet (60 mg)	1 tablet (60 mg)	120 mg
9 - < 12	1.5 tablets (90 mg)	1.5 tablets (90 mg)	180 mg
12 - < 17	2 tablets (120 mg)	2 tablets (120 mg)	240 mg
17 - < 20	2.5 tablets (150 mg)	2.5 tablets (150 mg)	300 mg)
20 - < 25	3 tablets (180 mg)	3 tablets (180 mg)	360 mg
25 - < 29	3.5 tablets (210 mg)	3.5 tablets (210 mg)	420 mg
29 - < 35	4 tablets (240 mg)	4 tablets (240 mg)	480 mg

Renal impairment: no dosage adjustment of abacavir is necessary in patients with renal dysfunction. However, abacavir should be avoided in patients with end-stage renal disease (see section 5.2).

Hepatic impairment: abacavir is primarily metabolized by the liver. No dose recommendation can be made in patients with mild hepatic impairment. No data are available in patients with moderate hepatic impairment, therefore the use of abacavir 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 (see section 5.2). Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).

Elderly: no pharmacokinetic data is currently available in patients over 65 years of age.

4.3 Contraindications

Abacavir Sulfate Oral Solution is contraindicated in patients with known hypersensitivity to the active substance (abacavir) or to any of the excipients. (See Special warnings and special precautions for use, Sections 4.4 and 4.8.)

Abacavir Sulfate Oral Solution is contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and special precautions for use

Hypersensitivity Reaction (also see section 4.8)
In clinical studies approximately 5% of subjects receiving abacavir developed a significant 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.

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 treatment history and resistance testing (see section 4.1).

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 the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or 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 characterized by the appearance of symptoms indicating multi-organ system involvement. *Almost all hypersensitivity reactions will have fever and/or rash as part of the clinical presentation*.

Other signs and symptoms may include:

- respiratory signs and symptoms such as dyspnea, sore throat, cough, and abnormal chest x-ray findings (predominantly infiltrates, which may be localized), any of which may lead to misdiagnosis of the abacavir hypersensitivity reaction as bronchitis, pharyngitis, or pneumonia
- gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain, any of which may lead to misdiagnosis of the abacavir hypersensitivity reaction as gastroenteritis or other condition presenting with abdominal or GI complaints.

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 abacavir therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical management of hypersensitivity reaction
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 (seen in clinic every two weeks), especially during the first two months of treatment with abacavir.

Patients who are diagnosed with a hypersensitivity reaction while on therapy MUST discontinue abacavir immediately.

Abacavir Sulfate Oral Solution, or any other medicinal product containing abacavir in any form 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 minimize 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 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). It is currently difficult to differentiate between rashes induced by these products and abacavir-related hypersensitivity reactions.

Manangement after an interruption of abacavir therapy
If treatment with abacavir in any form is discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, abacavir or any other medicinal product containing abacavir in any form 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. On very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and had no preceding symptoms of a hypersensitivity reaction. In both cases, restarting abacavir ***must*** be conducted in a setting where medical assistance is readily available.

Essential patient information regarding potential hypersensitivity reaction
Prescribers and dispensers must ensure that patients are fully informed regarding the following information on hypersensitivity reaction potential with abacavir:

- 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 abacavir again or any other medicinal product containing abacavir
- in order to avoid restarting abacavir, patients who have experienced a hypersensitivity reaction should be asked to return the remaining abacavir tablets or oral solution to the pharmacy
- patients who have stopped abacavir 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 abacavir regularly
- each patient should be reminded to read the package leaflet included in or with the abacavir packaging
- patients must be reminded of the importance of removing the Alert Card included in the packaging and keeping it with them at all times.

Lactic acidosis
Lactic acidosis is usually associated with hepatomegaly and hepatic steatosis, and 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 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.

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 hematological disorders (anemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviors). 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 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 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 hypothesized. 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 (see section 4.8).

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

Liver disease
The safety and efficacy of abacavir has not been established in patients with significant underlying liver disorders. Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3). Patients with chronic hepatitis B or C who are 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 to the relevant product information for these medicinal products.

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.

A pharmacokinetic study has been performed in patients with mild hepatic impairment. However, a definitive recommendation on dose reduction is not possible due to substantial variability of drug exposure in this patient population (see section 5.2). The clinical safety data available with abacavir in hepatically impaired patients is very limited. Due to the potential increases in exposure (AUC) in some patients, close 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 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 is contraindicated (see section 4.3).

Renal disease
Abacavir should not be administered to patients with end-stage renal disease (see section 5.2).

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, generalized and/or focal mycobacterium 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 CART. Patients must 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
Patients should be advised that current antiretroviral therapies have 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.

Triple nucleoside therapy
In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine, and zidovudine needs special consideration (see section 5.1).

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

Once daily administration (abacavir 600 mg)
The benefit of abacavir administered as a once daily regimen is mainly based on a study performed in combination with efavirenz and lamivudine, in antiretroviral-naïve adult patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 enzymes
Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for Cytochrome P450 enzyme-mediated interactions with other medicinal products involving abacavir is low. P450 does not play a major role in the metabolism of abacavir, and abacavir does not inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit CYP 3A4, CYP 2C9 or CYP 2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral PIs and other medicinal products metabolized by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

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

Ethanol
The metabolism of abacavir is altered by concomitant 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
In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir Cmax and a one hour delay in tmax but the AUC was unchanged. These changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22%. The induction of drug metabolizing enzymes cannot therefore be excluded. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing. Occasional methadone re-titration may be required.

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

4.6 Pregnancy and lactation

Abacavir is not recommended during pregnancy. The safe use of abacavir in human pregnancy has not been established. Placental transfer of abacavir and/or its related metabolites has been shown to occur in animals. Toxicity to the developing embryo and fetus occurred in rats, but not in rabbits (see section 5.3). The teratogenic potential of abacavir could not be established from studies in animals.

Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. There are no data available on the safety of abacavir when administered to babies less than three months old. It is therefore recommended that mothers do not breastfeed their babies while receiving treatment with abacavir. Additionally, it is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

No studies on the effects of abacavir on the ability to drive or operate machinery have been performed.

4.8 Undesirable effects

Hypersensitivity reactions
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 characterized 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 clinical presentation, 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. Signs and symptoms that occurred in at least 10 percent of patients are identified as “common.”

General
Common: Fever, lethargy, malaise
Also reported: edema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Skin
Common: rash, usually maculopapular or urticarial

Gastrointestinal
Common: nausea, vomiting, diarrhea, abdominal pain, elevated liver enzymes
Also reported: mouth ulceration, hepatitis, liver failure

Respiratory
Common: dyspnea, cough
Also reported: sore throat, adult respiratory distress syndrome, respiratory failure

Neurological/Psychiatric
Common: headache
Also reported: paresthesias

Musculoskeletal
Common: myalgia
Also reported: myolysis (rare), arthralgia, elevated creatine phosphokinase (CPK)

Other
Also reported: leukopenia, elevated creatinine levels, 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 reintroduced, leading to more severe hypersensitivity reactions or death. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with these symptoms.

Symptoms of abacavir hypersensitivity typically appeared within the first six weeks, with a median time to onset of 11 days after initiation of treatment. However, hypersensitivity reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations recommended at regular two-week intervals.

It is likely that intermittent therapy with abacavir will increase the risk of developing sensitization and therefore occurrence of clinically significant hypersensitivity reactions. Patients should be advised of the importance of taking abacavir regularly. Restarting abacavir following a hypersensitivity reaction will result in a prompt return of symptoms within hours. This recurrence of a 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 abacavir and must never be rechallenged with abacavir or any other medicinal product containing abacavir.

To avoid a delay in diagnosis and minimize 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, reactions to other medications, etc.).

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.

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 all 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.

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

Many of those listed below occur commonly (nausea, vomiting, diarrhea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of hypersensitivity reaction.

If abacavir 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 (see section 4.4.).

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.

Other Reactions
Many adverse reactions to abacavir have not been treatment limiting. The following convention has been used for their classification: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000).

Metabolism and nutrition
Common: anorexia

Nervous system
Common: headache

Gastrointestinal
Common: nausea, vomiting, diarrhea
Rare: pancreatitis

Skin and subcutaneous tissue
Common: rash (without systemic symptoms)
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

General
Common: fever, lethargy, fatigue

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

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 (CART) has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Laboratory abnormalities
In controlled clinical studies laboratory abnormalities related to abacavir treatment were uncommon, with no differences in incidence observed between abacavir-treated patients and the control arms.

4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir have been administered to 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 (see section 4.8), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside reverse transcriptase inhibitor, ATC Code: J05AF06.

Mechanism of action
Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. Abacavir is metabolized intracellularly to the active moiety, carbovir 5'- triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy *in vitro* in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, lamivudine and stavudine.

In vitro resistance: Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro*, requiring multiple mutations for a clinically relevant increase in EC50 over wild-type virus.

In vivo resistance (treatment-naïve patients): 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%). 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%).

In vivo resistance (treatment-experienced patients): 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 abacavir 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-1 RNA [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.

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 and antiretrovirals from other classes (e.g. PIs or NNRTIs) is unlikely.

Clinical Experience

The demonstration of the benefit of abacavir is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of abacavir 300 mg twice daily in combination with zidovudine and lamivudine.

Treatment-naïve adults
In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells. One randomized, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine, and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomized treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86%

versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (>100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicenter, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomized to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by study week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as-treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; -1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomized (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), and efavirenz (EFV) vs. ZDV/3TC/EFV vs. ZDV/3TC/ABC. After a median follow-up of 32 weeks, tritherapy with the nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26% of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm, and 13% on the 4-drug arm categorized as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorized as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

Treatment-naïve children
In a study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤ 400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).

Treatment-experienced adults
In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 log10 copies/ml at 16 weeks).

In heavily NRTI-pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

Treatment-naïve adults
The once-daily regimen of abacavir (600 mg) is supported by a 48 week multicenter, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV-infected patients. They were randomized to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. 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 favor 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.

Treatment-experienced patients
In study CAL30001, 182 treatment-experienced patients with virologic failure were randomized and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) 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 FDC 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 log10 copies/ml versus -1.83 log10 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 randomized to continue this regimen or switch to abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks. Results indicate that the FDC 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).

Clinical efficacy
The safety and efficacy of abacavir in a number of different multidrug combination regimens is still not completely assessed (particularly in combination with NNRTIs).
Abacavir penetrates the cerebrospinal fluid (CSF) (see section 5.2), and has been shown to reduce HIV-1 RNA levels in the CSF. However, no effects on neuropsychological performance were seen when abacavir was administered to patients with AIDS dementia complex.

5.2 Pharmacokinetic properties

Absorption
Abacavir is rapidly and well-absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following oral administration, the mean time (tmax) to

maximal serum concentrations of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation.

At therapeutic dosages (assessed based on 300 mg twice-daily), the mean (CV) steady state Cmax and Cmin of abacavir are approximately 3.00 μg/ml (30%) and 0.01 μg/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 μg.h/ml (29%), equivalent to a daily AUC of approximately 12.0 μg.h/ml. The Cmax value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir Cmax was approximately 4.26 μg/ml (28%) and the mean (CV) AUC∞ was 11.95 μg.h/ml (21%).

Food delayed absorption and decreased Cmax but did not affect overall plasma concentrations (AUC). Therefore, abacavir can be taken with or without food. Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution
Following intravenous administration, the apparent volume of distribution was about 0.8 L/kg, indicating that abacavir penetrates freely into body tissues. 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%. The observed values of the peak concentrations are 9-fold greater than the IC50 of abacavir of 0.08 μg/ml or 0.26 μM when abacavir is given at 600 mg twice daily.

Plasma protein binding studies *in vitro* indicate that abacavir binds at low to moderate levels (~49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Metabolism
Abacavir is primarily metabolized by the liver with approximately 2% of the administered dose being excreted via the kidneys as an unaltered 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. The metabolites are excreted in the urine.

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 feces.

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 (AUC24,ss + 32 %, Cmax24,ss + 99 % and Ctrough + 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. Additionally, the efficacy and safety of abacavir given once daily has been demonstrated in a pivotal clinical study (CNA30021) (See section 5.1, Clinical experience).

Liver impairment
Abacavir is primarily metabolized 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 the substantial variability of abacavir exposure.

Renal impairment
Abacavir is primarily metabolized 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. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience abacavir should be avoided in patients with end-stage renal disease.

Children
According to clinical trials performed in children abacavir is rapidly and well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. The recommended dose of abacavir for children (three months to 16 years) is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice daily in adults.

There are insufficient safety data to recommend the use of abacavir in infants less than three months old. The limited data available indicate that a dose of 2 mg/kg in neonates less than 30 days old provides similar or greater AUCs, compared to the 8 mg/kg dose administered to older children.

Elderly
The pharmacokinetics of abacavir have not been studied in patients over 65 years of age.

5.3 Preclinical safety data

Abacavir was not mutagenic in bacterial tests but showed activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir has a weak potential to cause chromosomal damage both *in vitro* and *in vivo* at high test concentrations.

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the thyroid glands of male rats, and the liver, urinary bladder, lymph nodes and subcutis of female rats.

The majority of these tumors 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 tumor 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.

In pre-clinical toxicology studies, abacavir treatment 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 metabolized has not been observed in man.

Mild myocardial degeneration in the hearts 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.

In reproductive toxicity studies, embryo and fetal toxicity have been observed in rats but not in rabbits. These findings included decreased fetal body weight, fetal edema, and an increase in skeletal variations/malformations, early intrauterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-fetal toxicity.

A fertility study in the rat has shown that abacavir had no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artificial strawberry and banana flavors, citric acid anhydrous, methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), noncrystallizing sorbitol solution, water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Store at room temperature, 68° to 77°F (20° to 25°C). May be refrigerated. Do not freeze. Store in the original container.

6.5 Nature and contents of container

240 mL bottle containing oral solution

7. SUPPLIER

Aurobindo Pharma, Ltd., Unit III, Survey No 313 & 314, Bachyupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India 500 072

8. DATE OF USFDA TENTATIVE APPROVAL

June 27, 2006

LABELING

PART 5—LABELING TEMPLATE FOR CUT/PASTE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING
Abacavir Sulfate Oral Solution

1. NAME OF THE MEDICINAL PRODUCT

Abacavir Sulfate Oral Solution

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml of Abacavir Sulfate Oral Solution contains the equivalent of 20 mg of abacavir

3. LIST OF EXCIPIENTS

Artificial strawberry and banana flavors, citric acid anhydrous, methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), noncrystallizing sorbitol solution, water

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION DATE

<EXP MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Store at room temperature, 68° to 77°F (20° to 25°C). May be refrigerated. Do not freeze. Store in original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Aurobindo Pharma, Ltd., Unit III, Survey No 313 & 314, Bachyupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India 500 072

12. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <number>

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

14. INSTRUCTIONS FOR USE

SCIENTIFIC DISCUSSION

DISCUSSION

Name of the Finished Pharmaceutical Product	Abacavir Sulfate Oral Solution
Supplier	Aurobindo Pharma, Ltd.
Active Pharmaceutical Ingredient (API)	Abacavir
Internal Nonproprietary Name	Abacavir
Pharmacotherapeutic Group (ATC Code)	J05AF06
Therapeutic Indication	Treatment of HIV-1 infection in combination with other antiretroviral agents

1. Introduction

Abacavir Sulfate Oral Solution is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Abacavir Sulfate Oral Solution is not indicated for use in patients with clinically significant hypersensitivity to abacavir or any of the components contained in the formulation.

It is recommended that therapy be initiated only on the advice of a physician or healthcare professional experienced in the diagnosis and management of HIV infection and related disease.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the U. S. President's Emergency Plan for AIDS Relief (PEPFAR).

Composition
Abacavir Sulfate Oral Solution is a clear to opalescent, yellowish, strawberry-banana flavored liquid. Each mL contains 20 mg of abacavir sulfate equivalent to 20 mg of abacavir. Inactive ingredients include artificial strawberry and banana flavors, citric acid anhydrous, methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), noncrystallizing sorbitol solution, and water. Abacavir Sulfate Oral Solution is a generic version of Ziagen® Oral Solution.

Control of active pharmaceutical ingredient (API)
Abacavir Sulfate Oral Solution is controlled as per specifications in the application and cGMPs, and is consistent with general USP requirements and product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are in line with the requirements of major internationally used pharmacopoeias and guidelines for tablets. The test methods have been adequately validated.

Stability
The following storage conditions were proposed:
a. 40 ± 2°C/75 ± 5% RH – Initial, 1, 2, and 3 months
b. 50 ± 2°C/ARH (Ambient Relative Humidity) – Initial, 1, 2, and 3 months
c. 30 ± 2°C/70 ± 5% RH – Long Term and Initial, 3, 6, 9, and 12 months for the bulk C/C.
d. 25 ± 2°C/60 ± 5% RH – Except for the 1 and 2 month test station, analysis is performed on demand.

Up to six months accelerated and long term stability data was provided. All results met proposed limits. Based on the stability data provided, the proposed expiration date of two years was found to be acceptable.

Conclusions
It is concluded that the data submitted ensure acceptable quality of the finished medicinal product when stored under the conditions specified on the label.

3. Assessment of Bioequivalence

Aurobindo Pharma Ltd. requested a waiver from bioequivalence testing as specified in the U. S. Code of Federal Regulations (CFR) Section 320.22 (b)(3). The reference listed drug (RLD) for Abacavir Sulfate Oral Solution is Ziagen® Oral Solution, sponsored by GlaxoSmithKline (GSK). The composition of the firm's Abacavir Sulfate Oral Solution does not differ significantly from the RLD. The waiver from *in vivo* bioequivalent study was granted by the USFDA Office of Generic Drugs Division of Bioequivalence.

4. Summary of Product Safety and Efficacy

4.1 Introduction

Background
Abacavir Sulfate Oral Solution has been shown to conform to the same appropriate standards of quality, efficacy, and safety as those required of the innovator's product. According to the submitted data on quality and bioavailability it is pharmacologically and therapeutically equivalent and thus interchangeable with the innovator product Ziagen® Oral Solution, for which benefits have been proven in terms of clinical efficacy.

Product Design
The development strategy for Abacavir Sulfate Oral Solution was concentrated on compatibility of the active pharmaceutical ingredient with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Clinical Safety
The clinical safety of this product is considered to be acceptable when the guidances and restrictions presented in the Summary of Product Characteristics (SPC, Part 4 of this Public Assessment Report), are taken into consideration. See the SPC, Section 4 ("Clinical Particulars") for extensive discussion of contraindications, special precautions, interactions, use in pregnancy, patient exposure (including overdosage), interactions, and adverse events.

Approved Indication
Abacavir Sulfate Oral Solution is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics

Abacavir is a nucleoside analogue with reverse transcriptase inhibition activity. Antiviral efficacy has been confirmed in primary cell cultures (mononuclear cells, macrophages) and in cell lines that are susceptibility to HIV-1 and HIV-2.

Data suggests implied synergism *in vitro* of abacavir with zidovudine, didanosine, and zalcitabine, and no observed antagonism with other drugs tested (lamivudine, amprenavir, and nevirapine).

Data from 327 adults (299 receiving abacavir) were used to define pharmacokinetics,

pharmacodynamics, and safety and dose range. In addition pharmacokinetic data in children from 3 months to 13 years of age were derived from two studies with the 4 and 8 mg/kg dosage regimens: one single dose study (n=22) and one study on the steady state pharmacokinetics (n=47).

Mutations associated with abacavir resistance selected during *in vitro* passage (K65R, L74V, Y115F, and M184V) have also been detected among isolates from subjects participating in clinical studies, with M184V and L74V being the most common. Treatment emergent mutations were less frequent when abacavir was given in combination with other antiretrovirals. In general, subjects harboring virus with wild-type RT genotype or 1-2 NRTI-associated mutations at baseline responded to abacavir with substantial decreases in plasma HIV-1 RNA while subjects with ≥3 NRTI-associated mutations had attenuated or no plasma HIV-1 RNA response to abacavir. The most common single RT mutation seen at baseline in these trials was the M184V, which has been associated with resistance to lamivudine. As described (see Clinical Efficacy, studies CNAB 3002, CNAAB 3003, CNAA 3006), abacavir as an add-on to treatment-experienced patients offers added antiretroviral activity irrespective of prior lamivudine therapy.

One possible explanation for the slightly better response in the lamivudine-experienced group (see Clinical Efficacy) is that the M184V mutation delays the emergence of resistance-conferring mutations and can resensitize resistant variants to zidovudine.

Pharmacokinetics

Following oral administration, abacavir is rapidly and extensively absorbed. Bioavailability is about 83% for the tablets. Once in the systemic circulation, abacavir distributes into extravascular space. Protein binding is approximately 50% and is independent of concentration. Based on radiolabeled studies, the drug readily distributes into erythrocytes. In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'glucuronide). The metabolites have no antiviral activity. *In vitro* experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations. Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of (14)C-abacavir: 83% of the radioactivity was recovered in urine, 1.2% as unchanged drug, 30% as the 5'-carboxylic acid metabolite, 36% as the 5'-glucuronide metabolite, and 15% as unidentified minor metabolites. Fecal elimination accounted for 16% of the dose. In single-dose studies, the observed elimination half-life was 1.54 +/- 0.63 hours.

Absorption and Distribution: Both the tablet (300 mg) and solution (20 mg/mL) formulations of abacavir lead to comparable systemic exposure. Food does not affect the overall exposure (single dose study of 300 mg, n=18). Plasma protein binding to human plasma is low to moderate (approximately 49% at therapeutic range).

It has been shown that abacavir penetrates cerebrospinal fluid. The clinical relevance of this finding is not established.

Abacavir is extensively bound to melanin-containing tissues. Abacavir was extensively distributed with higher concentrations in gastrointestinal tract, urinary tract, nasal turbinates, and uveal tissue of the eyes than in plasma.

Metabolism and elimination: Abacavir is extensively metabolized (alcohol dehydrogenase, UDP-glucuronyl transferase). Two major metabolites have been identified (5'-carboxylate and glucuronide). The metabolites and unchanged abacavir account for 83% of the administered abacavir dose in the urine and the remainder is eliminated in feces.

Abacavir is neither a major substrate nor an inhibitor of CYP3A4. Therefore, potent interactions are unlikely to occur with drugs that are substrates, inducers or inhibitors of this enzyme, which are numerous among concomitant medications commonly used by AIDS patients. There were two interaction studies: one with zidovudine + lamivudine and the second with alcohol. The results of those studies did not justify any specific dose recommendations. Products such as rifampicin, rifabutin and ritonavir that may induce UDP-glucoronyl transferase are not expected to clinically impact the exposure levels of abacavir. In an interaction study with ethanol, exposure levels of abacavir were
increased by about 41%, (clinically insignificant). Abacavir has no effect on the metabolism of ethanol. Retinoid compounds are eliminated via alcohol dehydrogenase and interaction with abacavir is possible but has not been studied.

Special populations
Children
Pharmacokinetic parameters of abacavir, following single or repeated doses, have been studied in 68 pediatric patients. Following multiple dose administration of abacavir at 8 mg/kg twice daily, mean steady-state AUC and Cmax were similar to those observed in adult patients. Also, analysis of actual and simulated pharmacokinetic data indicate comparable exposures after the administration of weight-based doses using the 300 mg scored tablets and the 8 mg/kg regimen using the oral solution in pediatric patients.

Hepatic impairment
- Mild: (Child Pugh score 5 to 6) showed a mean increase in abacavir half-life and AUC of 58% and 89%, respectively, following a single oral dose of 600 mg. A reduced dose of abacavir is recommended in patients with mild hepatic impairment.
- Moderate or severe: Abacavir pharmacokinetic parameters have not been assessed in these patients. Use of abacavir in these patients is *contraindicated*.

Elderly
Pharmacokinetic parameters of abacavir have not been studied in elderly patients. Since there is no effect of aging on alcohol dehydrogenase activity, it appears unlikely that aging will affect abacavir pharmacokinetics. The clinical data, although limited (31 patients > 50 years of age) offered reassurance that elderly patients are unlikely to have clinically significant pharmacokinetic alterations.

Renal impairment
Pharmacokinetic parameters of abacavir have not been studied in patients with renal impairment. Very limited data (6 patients) are available on pharmacokinetics from patients with end-stage renal disease (ESRD) indicating unaltered abacavir pharmacokinetics. Based on this limited experience, abacavir should be avoided in patients with ESRD

Drug interactions, related side effects and contraindications

Drug Interactions and related side effects
Because abacavir is metabolized via alcohol dehydrogenase, ethanol decreases the elimination of abacavir causing an increase in overall exposure to abacavir. In a study involving HIV-infected

men, coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC and a 26% increase in abacavir half-life. In males, abacavir had no effect on the pharmacokinetic properties of ethanol; this interaction has not been studied in females.

The pharmacokinetics of abacavir were not altered by the addition of either lamivudine, zidovudine, or a combined regimen of lamivudine + zidovudine. No clinically significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

In a study of 11 HIV-infected subjects receiving methadone maintenance therapy (40—90 mg/day) and abacavir 600 mg twice daily (twice the current recommended dose), methadone clearance increased by 22% (6—42%). While this interaction will not require dosage adjustment in the majority of patients, a small number of patients may require increased doses of methadone. In addition, a significant decrease in abacavir Cmax (34%) and increase in Tmax (67%) were noted, but no changes in overall abacavir clearance or half-life were reported. The clinical significance regarding abacavir therapy is unknown.

The co-treatment of HIV and Hepatitis C (HCV) has the potential to result in complex drug interactions. Cases of hepatic decompensation (some fatal) have occurred in patients co-infected with HIV and cirrhotic HCV who were receiving treatment with anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs), ribavirin, and alfa interferons (interferon alfa-2a, interferon alfa-2b, peginterferon alfa-2a, peginterferon alfa-2b). Patients with chronic, cirrhotic HCV co-infected with HIV receiving NRTIs and alpha interferons, with or without ribavirin, appear to be at increased risk for the development of hepatic decompensation (e.g., Childs-Pugh >= 6) compared to patients not receiving antiretroviral therapy. Closely monitor these patients for treatment associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered if medically appropriate. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation. In general, ribavirin and alfa interferons should not be administered to patients with chronic, cirrhotic HCV with hepatic decompensation who are co-infected with HIV before or during treatment. Additionally, nucleoside analogs have been associated with fatal and nonfatal lactic acidosis and hepatomegaly with or without steatosis and should be used cautiously in patients with hepatic disease. While ribavirin inhibits the phosphorylation reactions required to activate lamivudine, stavudine, and zidovudine, no evidence of a pharmacokinetic or pharmacodynamic interaction was seen. Ribavirin should not be used with didanosine as concurrent administration increases blood concentrations of didanosine and its active metabolite and coadministration has resulted in fatal hepatic failure and increased the incidence of other didanosine-related clinical toxicities.

Concurrent administration of tipranavir with abacavir results in decreased abacavir concentrations (40% reduction in AUC). The clinical significance of this interaction has not been established, and no recommendations for abacavir dosage adjustments are available.

Do not coadminister abacavir-containing products, including Ziagen®, Epzicom™, or Trizivir™.

Contraindications and precautions

Hypersensitivity
Abacavir Sulfate Oral Solution is contraindicated in patients with known hypersensitivity to the active substance (abacavir) or to any of the excipients. Abacavir has been associated with a fatal hypersensitivity reaction. To reduce the risk of hypersensitivity reactions, perform HLA-B*5701

testing before initiating an abacavir-containing treatment regimen. Do not prescribe/administer abacavir to an HLA-B*5701-positive patient, and clearly record the positive status as an abacavir allergy in the patient's medical record.

If HLA-B*5701 screening is not readily available, initiation of abacavir is reasonable with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction. Additionally, racial background is a risk factor for hypersensitivity, with Caucasian patients generally having a higher risk (5—8%) than Black patients (2—3%). Immediately discontinue abacavir in patients developing or with suspected signs or symptoms of abacavir hypersensitivity, including those presenting with 2 or more of the following signs or symptoms:

- Fever
- Rash
- Gastrointestinal (e.g., nausea, vomiting, diarrhea, abdominal pain)
- Constitutional (generalized malaise, fatigue, achiness)
- Respiratory (dyspnea, cough, pharyngitis)

Permanently discontinue abacavir if the clinical presentation of an acute illness cannot be clearly differentiated from a hypersensitivity reaction. ***Never*** reinitiate abacavir or an abacavir-containing product (e.g., Ziagen™, Epzicom™ (lamivudine + abacavir), or Trizivir® (abacavir + lamivudine + zidovudine)) in a patient who experiences a hypersensitivity reaction as more severe symptoms will recur within hours of administration and may include life-threatening hypotension and death.

Whenever abacavir is dispensed (i.e., new prescription OR prescription refill), a medication guide and warning card that provide information about recognition of hypersensitivity reactions should be dispensed with the drug.

Clinical reports indicate that severe or fatal hypersensitivity reactions can occur within hours after abacavir reintroduction in patients who have no identified history of, or who had unrecognized symptoms of, hypersensitivity to abacavir. In these reports, severe or fatal hypersensitivity occurred upon drug reintroduction after abrupt discontinuation for reasons unrelated to symptoms of hypersensitivity (e.g., interruption in drug supply or discontinuation of abacavir while treating other medical conditions). In some cases, symptoms consistent with hypersensitivity may have been present before abacavir was discontinued, but may have been attributed to other medical conditions (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications). In a minority of cases, hypersensitivity reactions occurred days to weeks after abacavir reintroduction. If abacavir has been discontinued for reasons other than symptoms of hypersensitivity and if reinitiation is being considered, re-evaluate the reason for discontinuation and ensure that the patient did not have any suspected symptoms of hypersensitivity. If hypersensitivity symptoms are suspected upon review, do not reinitiate abacavir. If symptoms consistent with hypersensitivity are not identified, reintroduce abacavir with caution. Patients should be made aware that a hypersensitivity reaction can occur upon reintroduction, and that reintroduction of abacavir therapy should only be undertaken if patients have ready access to medical care.

Obesity and prolonged nucleoside exposure
Obesity and prolonged nucleoside exposure may be risk factors for lactic acidosis and severe hepatomegaly with steatosis during nucleoside analog therapy. Fatalities have been reported with use of antiretroviral agents alone or in combination, including abacavir. A majority of these cases occurred in females.

Pregnancy and lactic acidosis/hepatic steatosis
It is unclear if pregnant women are at an increased risk for this syndrome. However, because pregnancy can mimic some of the early symptoms of lactic acid/hepatic steatosis syndrome or be associated with other significant disorders of liver metabolism, clinicians need to be alert for early diagnosis of this syndrome. Pregnant women receiving nucleoside analogs should have LFTs and serum electrolytes assessed more frequently during the last trimester and any new symptoms should be evaluated thoroughly.

Breastfeeding
Breastfeeding is not recommended by HIV-infected mothers to avoid the risk of postnatal transmission of HIV. HIV-infected mothers should be instructed not to breastfeed, even if they are receiving abacavir.

Liver Disease
Abacavir is *contraindicated* in patients with moderate to severe hepatic disease, as safety, efficacy, and pharmacokinetic parameters have not yet been established. In patients with mild hepatic disease (Child-Pugh score 5—6), a reduction in dose is required. Abacavir should be used with caution in patients with known risk factors for liver disease (e.g., alcoholism). However, cases of lactic acidosis or liver problems have been reported in patients with no risk factors. Treatment should be discontinued in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked increases in transaminases.

Myocardial infarction
In a published prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI) with the rate of MI decreasing within a few months after drug cessation. A second retrospective, observational study also showed an increased risk of MI when assessing cardiovascular disease (CVD) risk factors and suggested that the risk increased in those with higher underlying risk for CVD. Patients in both studies who started abacavir for the first time had worse initial cardiovascular risk profiles than observed with the other nucleoside reverse transcriptase inhibitor (NRTI) agents; therefore, it cannot be ruled out that some of these results could be the result of channeling bias. The authors of both studies speculate that the underlying mechanism for increased risk of CVD may be due to an increased propensity for subclinical atherosclerosis to manifest itself clinically as a consequence of the proinflammatory potential of abacavir. In contrast to these two observational trials, a sponsor-conducted, pooled analysis of clinical trials showed no excess risk of myocardial infarction in abacavir-treated subjects as compared with control subjects.

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

Clinical Efficacy

Compliance with abacavir therapy is favorable based on twice daily dosing and the absence of significant interaction with food.

The resistance pattern of abacavir appeared favorable since, in general, subjects harboring virus with wild-type RT genotype or 1-2 NRTI-associated mutations at baseline responded to abacavir with substantial decreases in plasma HIV-1 RNA. However, subjects with ≥ 3 NRTI associated mutations had attenuated or no plasma HIV-1 RNA response to abacavir. The most common single RT mutation at baseline in these trials in experienced patients was the M184V, which has been associated with resistance to lamivudine but not abacavir. Subjects harboring virus with the M184V alone have comparable HIV-1 RNA response to those with wild-type virus.

The dose rationale for adults has been sufficiently substantiated.

In therapy-naive patients, the durability of the antiviral effect of abacavir is mainly corroborated by long term results (Study CNAAB 3003). The virological response observed at week 16 in was sustained at week 48 (proportion of patients with undetectable viral load (400 copies/ml) is 77% and 71% respectively at week 16 and 48).

The limited proportion of switches in the abacavir arm confirms the virological impact of abacavir. At week 48, 71% of patients remained on treatment with abacavir. It should be emphasised that other studies (CNAB 2002, CNAA 2004 and CNAB 3009) underscored this durable impact on the viral load, but their interpretation is much more limited since there are open label studies and/or performed in few patients. No additional benefit has been demonstrated in terms of CD4 cell counts.

In therapy-experienced patients, short-term data (16w) from (CNAB 3002) 185 patients moderately exposed to previous antiretroviral therapy and moderately advanced (CD4 409 cells) provided the most information. Abacavir demonstrated a slight impact on the viral load (median change of viral load -0,44 log10 copies/ml). These results are in accordance with genotypic and phenotypic analyses, which demonstrate that ≥3NRTI mutations at baseline are not favorable for a response to abacavir. Information provided by other studies (CNAB 3009, CNAA 2007, ACTG 368 and ACTG 372) are limited since they are mainly open label studies and/or performed in few patients.

The dose rationale for children has been sufficiently substantiated. The pivotal placebo controlled trial performed in 205 children (CNAA 3006) demonstrated a superior effect (antiviral and on CD4 cells) of abacavir + lamivudine + zidovudine vs. lamivudine + zidovudine that seemed sustained over 24 weeks.

Clinical Safety

The major safety concern of abacavir is related to the 3% incidence of hypersensitivity reactions which have been described in more than 600 patients. This is a potentially life threatening condition with hypotension and multi-organ involvement. The mortality rate from hypersensitivity reactions is 0.014% (3/21000). A majority of cases of hypersensitivity reaction (94%) appear within the first 6 weeks of abacavir treatment but 6% of cases appear after 6 weeks of treatment.

Rechallenge with abacavir therapy after an episode of hypersensitivity confers a 35% risk of life threatening consequences. Of the 636 patients with hypersensitivity reactions, 63 (10%) were rechallenged with abacavir in the overall database. Although various precautionary measures have reduced the risk of rechallenge with abacavir, the risk of rechallenge remains at about 6%.

In children, the major safety concern is hypersensitivity reaction. In this population,

hypersensitivity reactions are particularly difficult to identify, particularly in very young children.

See Summary of Product Characteristics, Part 4.4 ("Special warnings and special precautions") for extensive discussion of clinical safety parameters.

5. Overall conclusion and benefit risk assessment

Quality
The quality of Abacavir Sulfate Oral Solution is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4 of this Public Assessment Report). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Abacavir Sulfate Oral Solution has been shown to be bioequivalent to the comparator product, Ziagen® Oral Solution.

Efficacy and Safety
Abacavir Sulfate Oral Solution is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment
Based on USFDA assessment of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Abacavir Sulfate Oral Solution was considered acceptable for the following indication: HIV-1 infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA tentative approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **tentatively approved** indicates that although existing patents and/or other marketing exclusivity prevent marketing of this product in the USA, the product meets all of USFDA's safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

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