VI.1 Elements for a public summary

VI.2.1 Overview of disease epidemiology

HIV (human immunodeficiency virus) infection

Human immunodeficiency virus is a virus that causes acquired immunodeficiency syndrome (AIDS). It targets the immune system and especially white blood cells that defend the human body against infections. As the infection with HIV progresses the immune system weakens and leaves the body vulnerable to other infections.

In 2012 an estimated 35.3 million people were living with HIV. Sub-Saharan Africa, especially southern Africa, has the highest global burden of HIV. HIV prevalence is increasing worldwide because people on antiretroviral therapy are living longer, although new infections decreased from 3.3 million in 2002, to 2.3 million in 2012. Global AIDS-related deaths peaked at 2.3 million in 2005, and decreased to 1.6 million by 2012. An estimated 9.7 million people in low-income and middle-income countries had started antiretroviral therapy by 2012.[1]

VI.2.2 Summary of treatment benefits

HIV is a complex disease with effects which change over time. There is no single best treatment for HIV infection and people who have been taking medicines for a while to treat HIV infection may have to change treatment. The drug combination a person is taking might change over time either because of side effects or because the drugs become less effective.

In the studies, one of the main measures of how well abacavir and lamivudine worked was levels of HIV. White blood cells (called CD4 T-cells) were also counted to see how well abacavir and lamivudine worked. HIV kills CD4 T-cells, which help the body fight infections. In ABC studies, ABC led to lower levels of HIV, particularly when ABC was included in combination treatment. It also reduced the virus level as well as other medicines used to treat viruses.

VI.2.3 Unknowns relating to treatment benefits

No data are available in patients with moderate to severe liver disease

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reaction, including the danger that a negative result on a gene test will lead to a failure to diagnose an allergic reaction. (ABC hypersensitivity reaction, including reduced vigilance following HLA-B*5701 testing).	Overall, about five of 100 people given ABC without gene testing developed an allergic reaction. Approximately five or six of every 10 patients who have the gene associated with ABC allergy will have an allergic reaction. Of those who do not	There is a test for a gene that is very common in people who have an allergic reaction to ABC. Use of this test to determine who will get ABC reduces the chance the drug will be given to someone who will have an allergic reaction.

Risk	What is known	Preventability
	have the gene, no more than four in 100 will have an allergic reaction. Most people with allergic reaction develop fever and rash. However, many other body systems can be affected. Patients may have nausea, vomiting, diarrhoea, and abdominal pain (can occur anywhere in the stomach area between the chest and groin). Patients may also have cough, sore throat, problems breathing, and signs of lung problems on a chest x-ray. Allergic reactions can also cause people to feel tired, generally ill, or have pain in their muscles or joints. Symptoms of an allergic reaction can develop at any time during ABC treatment. They usually happen during the first 6 weeks after the first dose of ABC. If the drug is not stopped, symptoms get much worse and can lead to death.	However, people can have an allergic reaction even if the test does not show that the person has the gene. Stopping ABC usually stops the allergic reaction. Starting ABC again in a patient who has had an allergic reaction is very dangerous, even if the gene test does not show the presence of the gene. An 'alert' card is included in every pack of ABC medicine which the patient can carry with them. This describes the symptoms of the allergic reaction.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in people with liver problems (Use in subjects with moderate/severe hepatic impairment)	Liver problems cause the body to process ABC differently. People with mild liver problems may be exposed to almost two times as much ABC as people with normal livers, even though they take the same dose. Also, it may take the drug about one and a half times longer to leave their bodies. People with HIV have liver problems at least one and a half times as often as people in general. The rate may be as much as four times higher. People who have hepatitis or abuse drugs by injection or who abuse alcohol are more likely to have liver problems than other people.

Risk	What is known (Including reason why it is considered a potential risk)
	People with moderate and severe liver problems should not receive ABC. If ABC is used in people with mild liver problems then close monitoring is required. People with severe liver problems should not receive ABC.
Risk of cancer in patients who take HIV drugs such as ABC for a long time (Long term risk of carcinogenicity)	Studies in mice and monkeys have shown that higher rates of cancer are possible with antiretroviral drugs (drugs for HIV, like ABC). There is not enough information to show cancer rates in adults or children who take antiretroviral drugs for a long time. One study which followed 12,069 adult patients for up to 5 years found no increase in death rate with long term HIV treatment. Studies that were up to 8 years long showed that children who took highly active antiretroviral drugs did not have increased rates of cancer. One study showed that the rates of cancer seemed to go down the longer children were exposed.
Use in pregnant women (Use in pregnancy)	There are no data on the use of abacavir/lamivudine in pregnancy, however, the risk of harm to unborn baby is unlikely in humans.
Heart attacks and other effects on blood supply to the heart muscle (Ischaemic cardiac events)	In one study, the risk of having a heart attack in people who had taken ABC recently was almost twice as high compared to people who had not recently taken ABC. In another study, an increase in the risk of having a heart attack was seen in patients who had recently taken ABC but was much smaller. In that study, patients who were enrolled more recently did not have an increase in heart attacks. No increased risk of heart attack with ABC was found in other studies. Conditions that generally increase the risk of heart disease such as smoking, diabetes, high blood lipid levels, and high blood pressure probably also affect the risk of heart disease in people taking ABC. Long-term use of antiretroviral drugs (drugs for HIV), also increases the risk of heart attacks. It is not clear if there is a higher risk of heart problems with ABC treatment or why this might occur.
Possible interaction of abacavir with ribavirin (medicine used to treat hepatitis C) (Possible interaction of abacavir with ribavirin)	This potential interaction might lead to a lesser chance for a good therapeutic response to ribavirin in hepatitis C and HIV co-infected patients. Nevertheless, reports in literature on this suspected interaction are conflicting. No causal relation has been established yet.

Risk	What is known (Including reason why it is considered a potential risk)
Possible interaction of abacavir with tenofovir (another medicine used to treat HIV infection) (Possible interaction of abacavir/3TC with tenofovir disoproxil fumarete)	This interaction may cause worse response to therapy of HIV infection in patients who were taking abacavir/ lamivudine and tenofovir concomitantly.
Risk of shorter time to virological failure – a state when the therapy fails to suppress and sustain a patient's viral load (number of viruses) to less than 200 copies/mL (Risk of shorter time to virological failure)	All antiretroviral therapies carry the risk of virological failure, when the therapy does not work properly and it does not suppress the number of viruses in blood sufficiently. This risk might be higher with abacavir/ lamivudine than with other therapeutic options.

Missing information

None

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Additional risk minimisation measures are for the following risk:

Allergic reaction to abacavir (Abacavir hypersensitivity reaction)

Risk minimisation measure(s): Educational materials – a slide deck, a website and an alert card
Objective and rationale: Healthcare professionals to understand the risk of hypersensitivity reaction and the need for HLA-B*5701 testing before the start of the therapy. Patients to be informed about the risk of developing a hypersensitivity reaction.
Summary description of main additional risk minimisation measures • HCPs educational materials to be provided to prescribing physicians to convey the following key messages regarding hypersensitivity reaction:

- ✓ Major symptoms associated with the hypersensitivity reaction
- ✓ Risk factors
- ✓ Recommendation for HLA-B*5701 screening
- ✓ Information on HLA-B*5701 testing
- ✓ Management of hypersensitivity reaction

- A website will be available for further education of healthcare professionals.
- An alert card to make patients aware about the risk of developing a serious allergic reaction which can be life-threatening.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Aggregate review of spontaneous cases or reports from the published literature of suspected ABC HSR (category 3)	Further characterise the features of HSR and the impact of HLAB* 5701 screening in the real world setting on the incidence of all suspected ABC HSR and rechallenge to ABC. To detect any possible new features of HSR, or changing trends in circumstances around HSR (e.g., incidence and reasons for rechallenge). Aim is to update the product label or initiate further pharmacovigilance actions if any	Abacavir hypersensitivity reaction	Planned for the next PSUR	Next DLP for PSUR is 31/12/2019

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	relevant safety information from these actions becomes available.			
Annual review of all reported HSR cases in member states where the product is marketed (category 3)	Further characterise the features of HSR and the impact of HLAB* 5701 screening in the real world setting on the incidence of all suspected ABC HSR and rechallenge to ABC. To detect any possible new features of HSR, or changing trends in circumstances around HSR (e.g., incidence and reasons for rechallenge). Aim is to update the product label or initiate further pharmacovigilance actions if any relevant safety information from these actions becomes available.	Abacavir hypersensitivity reaction	Planned yearly after the registration process is finalised	First review will be performed one year after the finalisation of the registration process. One yearly thereafter.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable as this is the initial version.

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	23/06/2016	Important identified risks: • Hypersensitivity reaction • Hepatotoxicity Important potential risks • Mitochondrial dysfunction • Immune reactivation syndrome • Osteonecrosis • Myocardial infarction • Carcinogenicity (associated with abacavir) Missing information • Use in elderly • Use in patients with moderate and severe hepatic impairment • Use in children weighting less than 25 kilograms • Use in pregnancy and breastfeeding	N/A
1.1	31/01/2017	Important identified risks: • Abacavir hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) Important potential risks • Use in subjects with moderate/ severe hepatic impairment • Long term risk of carcinogenicity and long term exposure to NRTIs • Use in pregnancy • Ischaemic cardiac events • Possible interaction of abacavir with ribavirin • Possible interaction of abacavir/3TC with tenofovir disoproxil fumarete • Risk of shorter time to virological failure Missing information None	RMP was updated based on comments raised within the registration process. List of safety concerns was updated in order to be in line with the reference product. Additional PhV activity in a form of aggregated review of all reports of abacavir hypersensitivity reactons was added. Additional risk minimisation measures were reviewed to include education materials for physicians in a form of slide deck and a website.
1.2	19/05/2017	Important identified risks: • Abacavir hypersensitivity reaction (including reduced	As suggested by assessor, Patient Alert Card will be provided within the packs,

Version	Date	Safety Concerns	Comment
		vigilance following HLA-B*-5701 testing) <u>Important potential risks</u> • Use in subjects with moderate/ severe hepatic impairment • Long term risk of carcinogenicity and long term exposure to NRTIs • Use in pregnancy • Ischaemic cardiac events • Possible interaction of abacavir with ribavirin • Possible interaction of abacavir/3TC with tenofovir disoproxil fumarete • Risk of shorter time to virological failure <u>Missing information</u> None	as a tearaway portion from the PIL. RMP has been amended in all the concerned parts to report the correct information.