VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Human immunodeficiency virus (HIV) is a virus that attacks your body's natural defense system and causes acquired immunodeficiency syndrome (AIDS). HIV is most commonly passed on by sexual contact but one can also become infected following infected blood transfusions, needle sharing. It can be passed to an unborn child from a HIV-positive mother. Nearly 110,000 people living with HIV in the UK are diagnosed with HIV and approximately 26,000 people living with HIV in the UK have not yet been diagnosed. Black African people make up 1.9% of the UK population but 36% of all people living with HIV. Around 1 in 17 men who have sex with men living in the UK has HIV. In 2013 less than 1% of people with HIV died.

VI.2.2 Summary of treatment benefits

Abacavir/Lamivudine 600mg/300mg is a medicine that contains two active substances, Abacavir (600 mg) and Lamivudine (300 mg). Abacavir/Lamivudine is used in combination with at least one other medicine which acts against viruses to treat patients over 12 years old who are infected with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS). It does not completely cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood which are a type of blood cells that are important in helping your body to fight infection. Clinical experience with the combination of abacavir and lamivudine as a once daily regimen was mainly based on six studies with a total of 2,696 adult patients. A further study was done where different amounts of abacavir and lamivudine combinations were compared. In the studies, one of the main measures of how well abacavir/ lamivudine worked was levels of HIV. White blood cells (called CD4 T-cells) were also counted to see how well abacavir worked. HIV kills CD4 T-cells, which help the body fight infections.

In abacavir studies, abacavir led to lower levels of HIV, particularly when abacavir 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

In the followings cases; safety and treatment benefits are unknown. No data are available in patients with moderate hepatic (liver) impairment, therefore the use of Abacavir/Lamivudine is not recommended unless judged necessary. In patients with mild and moderate hepatic (liver) impairment monitoring of Abacavir plasma levels is recommended. Abacavir/Lamivudine must not be used in patients with severe hepatic (liver) impairment. Special care is advised in patients over 65 years of age due to age associated changes such as the decrease in renal (kidney) function and alteration of haematological (blood) parameters. Abacavir/Lamivudine is not recommended for the treatment of children less than 12 years of age as the safety and effectiveness of the medicine has not yet been established. There are no data on the use of Abacavir/Lamivudine in pregnancy. Lamivudine is excreted in human milk. It is expected that Abacavir will also be excreted into human milk, although this has not been confirmed. As a general rule, it is recommended that mothers infected with HIV do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

VI.2.4 Summary of safety concerns

Table 8: 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. (Abacavir 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 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 andcan lead to death.	1. Incidence of hypersensitivity (allergic reaction) can be reduced. 2. Patients who have a gene HLAB* 5701 are more likely to develop an allergic reaction to Abacavir/Lamivudine. Patients should be tested for this gene before starting treatment with Abacavir/Lamivudine. 3. Doctors should be aware that Abacavir/Lamivudine, or any other medicinal product containing Abacavir, must never be restarted in patients who have stopped therapy due to a hypersensitivity (allergic) reaction. 4. Hypersensitivity (allergic) 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. HCPs should take care that such patients should be monitored closely, especially during the first two months of treatment with Abacavir/Lamivudine, with consultation every two weeks. An ‘alert card’ is included in every pack of Abacavir/Lamivudine, which the patient should carry with them at all times. This describes the symptoms of the allergic reaction. 5. Abacavir/Lamivudine or any other medicinal product containing Abacavir, must never be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting Abacavir following a hypersensitivity reaction may result in a prompt return of symptoms within hours.

Table 9: Important potential risks

Risk	What is known
Risk of heart attack (Ischaemic cardiac events)	In one study, the risk of having a heart attack in people who had taken abacavir recently was almost twice as high compared to people who had not recently taken abacavir. In another study, an increase in the risk of having a heart attack was seen in patients who had recently taken abacavir 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 abacavir 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 abacavir. 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 abacavir treatment or why this might occur.
Shorter time until abacavir/lamivudine becomes ineffective as HIV treatment (Shorter time to virological failure)	Patients taking abacavir/ lamivudine may experience virological failure sooner than those taking other drug combinations. There are mixed opinions on why this may be including, the way the body breaks the drug down, because the drug was not taken correctly by the patient or the virus has becomes resistant to KIVEXA.
Possible interaction of abacavir/lamivudine with tenofovir disoproxil fumarate	There is a risk of virological failure (treatment failure) when Abacavir/Lamivudine is used concomitantly (along with) a medication called tenofovir disoproxil fumarate.
Use in pregnancy	So far, children born to women who received ABC/3TC during pregnancy have not shown increases in birth defects. About three in every 100 women who were exposed during the first trimester of pregnancy have given birth to babies with birth defects. This rate was the same if the drug was taken in the second or third trimester. This rate is the same as seen with other similar HIV therapies. One study, in rats, showed that pregnant rats who took ABC in high doses gave birth to rats with birth defects. The levels of drug in the mother rats' bodies were more than10 times higher than levels in people taking the usual dose of ABC (600 mg). Studies in rabbits did not show any birth defects
Risk of cancer in patients who take HIV drugs such as ABC for a long time (Long term risk of carcinogenicity and long term exposure to NRTIs)	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 patients with liver impairment (Use in patients with moderate/severe hepatic impairment)	People with moderate and severe liver problems should not receive abacavir. If abacavir is used in people with mild liver problems then close monitoring is required. People with severe liver problems should not receive abacavir.

Table 10: Missing information

Risk	What is known
None	Not applicable

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. The Summary of Product Characteristics and the Package leaflet for Abacavir and Lamivudine can be found in the EPAR page.

Additional risk minimisation measures are for the following risk:

Abacavir Hypersensitivity Reactions
Risk minimisation measures: • An alert card for Abacavir Hypersensitivity Reaction for patients being treated with Abacavir and Lamivudine film-coated tablets. Ongoing provision of this with all prescriptions. • Provision of Abacavir Hypersensitivity Reaction education materials for HCPs in form of a slide set will be distributed as required by the local competent authority. • A website for Abacavir Hypersensitivity Reaction for HCPs to treat patients with Abacavir and Lamivudine film-coated tablets will be made available. The mock-up of the proposed website page has been provided within the RMP as Annex 11c. • All prescribers and dispensing pharmacists of Abacavir/Lamivudine 600mg/300mg film-coated tablets will have access to the Educational material for HCPs. The way of distribution and if required the content of the national educational material will be aligned with the national Authorities according to the nationally present conditions and requirements. The patient alert card will be delivered to patients by HCPs with the prescriptions but when dispensed. • Effectiveness will be evaluated by annual assessing the frequency and severity of the reports of Abacavir hypersensitivity reaction in the member states in which the product is marketed.
Objective and rationale: To increase understanding and awareness of abacavir HSR.
Summary description of main additional risk minimisation measures: An alert card for Abacavir Hypersensitivity Reaction for patients being treated with Abacavir and Lamivudine film-coated tablets. Provision of Abacavir Hypersensitivity Reaction education materials for HCPs in the form of a slide set will be distributed as required by the local competent authority. A website for Abacavir Hypersensitivity Reaction for HCPs to treat patients with Abacavir and Lamivudine film-coated tablets will be made. The mock-up of the proposed website page has been provided within the RMP as Annex 11c.

Abacavir Hypersensitivity Reactions

All prescribers and dispensing pharmacists of Abacavir/Lamivudine 600mg/300mg film-coated tablets will have access to the Educational material for HCPs. The way of distribution and if required the content of the national educational material will be aligned with the national Authorities according to the nationally present conditions and requirements. The patient alert card will be delivered to patients by HCPs with the prescriptions but when dispensed.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comments
V1.1	29 September 2016	No changes to the list of safety concerns.	RMP version was changed from V1 to V1.1 based on request from BfArM (during the validation phase) in order to reflect the current QPPV name.
V1.2	21 March 2017	Changes in safety concerns as follows: **Important identified risk** Abacavir Hypersensitivty Reaction expanded to 'ABC hypersensitivity reaction, including reduced vigilance following HLA-B*5701 testing'. Hepatic impairment (considered as an important identified risk in previous RMP version) amended to "Use in patients with moderate/ severe hepatic impairment" and considered as an **Important Potential risk**.	Safety concerns are aligned based on assessors comments. Part II (Module SI – SVII) deleted from the RMP. Details regarding the additional risk minimisation measure for 'Abacavir hypersensitivity reaction, including reduced vigilance following HLA-B*5701 testing' updated in the relevant sections of the RMP. Changes done in the list of safety concerns are reflected in all the revelant sections of the RMP. Part III (Pharmacovigilance plan) updated. Text updated in Summary of treatment benefits and summary of safety concerns. Change in the numbering of Annex done throughout the RMP. Pregnancy follow-up form added in Annex 7. Signatory page introduced based on updated Glenmark RMP template.

Version	Date	Safety concerns	Comments
			List of abbreviation updated, Minor grammatical and formatting changes done in the RMP. Changes in SmPC and PIL are proposed.

V1.3	10 July 2017	Changes in safety concerns as follows: **Important potential risk:** Drug Interaction with Ribavirin was removed. Drug interaction with Tenofovir Disoproxil Fumarate was expanded to “Possible interaction of abacavir/lamivudine with tenofovir disoproxil fumarate”. Use during pregnancy and breastfeeding was amended to “Use in pregnancy” Carcinogenicity and long term use was modified to “Long term risk of carcinogenicity and long term exposure to NRTIs”	Safety concerns are updated based on assessor’s comments (NL; Day 145 Comments) to alingn with reference product. Annex 10 was updated to align with the reference product (NL; Day 145 Comments) and as per Glenmark internal processes. Changes done in the list of safety concerns and Annex 10 are reflected in all the revelant sections of the RMP. Minor grammatical and formatting changes done in the RMP.