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 1.8% of the UK population but 36% of all people living with HIV. Around 1 in 17 men who have sex with men (MSM) 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.

Abacavir/Lamivudine has been studied in three main studies involving a total of 1,230 patients. The studies compared Abacavir taken at a dose of 600 mg once a day and at a dose of 300 mg twice a day, in combination with lamivudine and one or two other antiviral medicines. Two studies used the active substances taken as separate medicines, while the third used a combination tablet for the once-daily dose. Both doses of Abacavir, taken in combination with lamivudine and other antiviral medicines, were equally effective in reducing viral loads. The combination tablet taken once a day was also as effective as the medicines taken separately twice a day in reducing viral loads over 24 weeks of treatment.

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

VI.2.4.1 Summary of safety concerns for identified risk

Table No: VI.2.4.1

Risk	What is known	Preventability
Abacavir Hypersensitivity (Allergic reaction) Reaction	Hypersensitivity (allergic reaction) reaction is an allergic reaction. Abacavir/Lamivudine is not recommended in patients who are allergic to the other ingredients present in Abacavir/Lamivudine tablets.	1. Incidence of hypersensitivity (allergic reaction) can be reduced. 2. Patients who have a gene HLA-B*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

Risk	What is known	Preventability
		may result in a prompt return of symptoms within hours.
Use in patients with hepatic (liver) impairment	Liver damage is known to occur in some patients with HIV and can be caused by some medicines used to treat HIV and by other infections such as hepatitis (inflammation of liver) B or C; however, the extent of liver damage varies widely. Abacavir/Lamivudine is contraindicated in patients with severe liver disease. No data are available in patients with moderate liver disease. Patients are instructed to inform their HCPs if they have some liver disease including hepatitis (inflammation of liver) B. If a patient has liver disease, including hepatitis B or C, Abacavir/Lamivudine film coated tablets should not be stopped without doctor's advice, as hepatitis (inflammation of liver) may come back.	1. Incidence of use of Abacavir/Lamivudine in patients with severe liver disease can be reduced. 2. Patients are advised to check with their doctors before taking Abacavir/Lamivudine, if they have any liver problem.

VI.2.4.2 Summary of safety concerns for potential risks

Table No: VI.2.4.2

Risk	What is known
Ischaemic cardiac events (risk of heart attack)	Abacavir may increase the risk of heart attack. Patients are instructed to inform their doctor if they have heart problems, if they smoke, or have other illnesses that may increase the risk of heart disease such as high blood pressure, or diabetes.
Risk of shorter time to virological failure (treatment failure)	There have been reports of a high rate of virological failure (treatment failure), and of emergence of resistance (no response to treatment medications) at an early stage when Abacavir and Lamivudine were combined with medications like Tenofovir Disoproxil fumarate taken together once a day.
Drug interaction with Ribavirin	Abacavir may make Ribavirin less effective at reducing levels of hepatitis C virus (a type liver problem) in the body. Patients should inform their doctor if they are taking a medication called Ribavirin.

Risk	What is known
Drug interaction 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 and lactation	Abacavir/Lamivudine is not recommended for use during pregnancy. Abacavir/Lamivudine and similar medicines may cause side effects in unborn babies. If you become pregnant while you're taking Abacavir/Lamivudine, your baby may be given extra check-ups (including blood tests) to make sure it is developing normally. If you are pregnant, if you become pregnant, or if you're planning to become pregnant talk to your doctor immediately about the risks and benefits of taking Abacavir/Lamivudine, or other medicines for treating HIV infection, during your pregnancy. Women who are HIV-positive must not breast-feed, because HIV infection can be passed on to the baby in breast milk. If you're breast-feeding, or thinking about breast-feeding. Talk to your doctor immediately.
Carcinogenicity (malignant tumour causing effect) and long term use	The carcinogenic potential (malignant tumour causing effect) of a combination of Abacavir and Lamivudine has not been tested.

VI.2.4.3 Summary of safety concerns for missing information

None

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the PIL. The measures in these documents are known as routine risk minimisation measures.
The SmPC and the PIL for Abacavir/Lamivudine tablets can be found in the Abacavir/Lamivudine 600mg/300mg Film-coated Tablets' 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. • A website for Abacavir Hypersensitivity Reaction for HCPs to treat patients with Abacavir and Lamivudine film-coated tablets. 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 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 re-challenge to ABC. To detect any possible new features of HSR, or changing trends in circumstances around HSR (e.g., incidence and reasons for re-challenge). Aim is to update the product label or initiate further pharmacovigilance actions if any relevant safety information from these actions becomes available. Spontaneous cases and data from the published literature are considered suitable source of information to achieve the objectives.
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. A website for Abacavir Hypersensitivity Reaction for HCPs to treat patients with Abacavir and Lamivudine film-coated tablets. 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.

VI.2.6 Planned post authorisation development plan (if applicable)

Not Applicable.

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

Version	Date	Safety Concerns	Comments
1.0	15 December 2014	Important identified Risk: • Abacavir Hypersensitivity Reaction • Lactic acidosis	RMP prepared for the first time

Version	Date	Safety Concerns	Comments
		• Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate Missing information: • Use in pregnancy and lactation • Carcinogenicity and long term use	
1.1	24 August 2015	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	The RMP has been updated in line with the comments received from assessor: Attaching educational material Contents of RMP revised in line with the updated SmPC and PIL Sections V.3; section VI.1.4; Summary table of risk minimisation measures updated Section VI.2.7; Summary of changes to the risk management plan over time updated
2.0	12 November 2015	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil	The RMP has been updated to make amendments to the planned date of assessment.

Version	Date	Safety Concerns	Comments
		Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	
2.1	01 December 2015	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	The RMP has been updated to incorporate changes reflected in the updated SmPC.
3.0	26 February 2016	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	The RMP has been updated in line with the comments received from assessor: • The RMP has been updated to incorporate the commitment of a website for Abacavir Hypersensitivity Reaction for health care professionals to treat patients with Abacavir and Lamivudine film-coated tablets. • The RMP has been updated to reflect that mention the ways of distribution

Version	Date	Safety Concerns	Comments
			of the educational material. • Annex 10 and Annex 11a, 11b has been updated as per the comments received.
3.1	07 April 2016	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	• The RMP has been updated in line with the assessor comments to provide a draft website for Abacavir Hypersensitivity Reaction (HSR) for HCPs to treat patients with Abacavir/Lamivudine film-coated tablets. The mock-up of the proposed website page has been provided within the RMP as Annex 11d. • The slide set (Annex 11b) of the RMP has been updated and has been drafted similar to the latest version of educational material of the reference listed product. • A Flowchart has been included in the educational material (Annex 11c) to facilitate the understanding of HCPs regarding the requirement of HLA-B*5701 testing to reduce Abacavir-HSR in existing and new patients on Abacavir therapy. • The mock-up of the proposed website page for Abacavir Hypersensitivity Reaction has been

Version	Date	Safety Concerns	Comments
			provided within the RMP as Annex 11d.
4.0	15 April 2016	Important identified Risk: • Abacavir Hypersensitivity Reaction • Use in patients with hepatic impairment Potential Risks: • Ischaemic cardiac events • Risk of shorter time to virological failure • Drug interaction with Ribavirin • Drug interaction with Tenofovir Disoproxil Fumarate • Use in pregnancy and lactation • Carcinogenicity and long term use Missing information: None	• The RMP has been updated in line with the assessor comments to delete the flowchart which was previously included in the educational material as Annex 11c. • Renaming of the Annex - mock-up of the proposed website page for Abacavir Hypersensitivity Reaction, which has now been renamed as Annex 11c. This was previously mentioned as Annex 11d.