VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Abacavir/lamivudine is used for antiretroviral combination therapy of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg.
Human immunodeficiency virus (HIV) is a virus typically transmitted via sexual intercourse, shared intravenous drug paraphernalia (needles), and mother-to-child transmission, which can occur during birth or during breastfeeding. HIV infects cells in the human immune system. That causes the immune system to weaken and the body to become less resistant to life-threatening infections. When the immune system is damaged enough that significant opportunistic infections begin to develop, the person is considered to have an advanced HIV infection, also known as AIDS (acquired immunodeficiency syndrome).
Globally, 35.3 million [32.2–38.8 million] people were living with HIV at the end of 2012.

VI.2.2 Summary of treatment benefits

Abacavir/lamivudine contains two active ingredients that are used to treat HIV infection: abacavir and lamivudine. These belong to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs)*. They work by interfering with the normal working of enzymes that are essential for the viruses to reproduce themselves.
Abacavir/lamivudine 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. CD4 cells are a type of white blood cells that are important in helping your body fight infection.
The fixed-dose combination tablet of abacavir/lamivudine (FDC) has been shown to be equivalent to lamivudine and abacavir administered separately. This was demonstrated in a study of FDC versus 2 x 300 mg abacavir tablets plus 2 x 150 mg lamivudine tablets.
If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, abacavir/lamivudine can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Abacavir/lamivudine is not recommended for the treatment of children weighing less than 25 kg as the necessary dose adjustment cannot be made.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reaction to abacavir (ABC hypersensitivity reaction(including reduced vigilance following HLA-B*-5701 testing)	You are more likely to develop this reaction if you have a gene called HLA-B*5701 (but you can get a reaction even if you don't have this gene). You should have been tested for this gene before abacavir/ lamivudine was prescribed for you. If you know you have this gene, tell your doctor before you take	Contact your doctor immediately: • if you get a skin rash, OR • if you get symptoms from at least 2 of the following groups: - fever - shortness of breath, sore throat or cough - nausea or vomiting, diarrhoea

Risk	What is known	Preventability
	abacavir/lamivudine. About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did **not** have a gene called HLA-B*5701 developed a serious allergic reaction. Anyone taking abacavir/ lamivudine could develop a hypersensitivity reaction to abacavir, which could be life threatening if they continue to take abacavir/lamivudine. The most common symptoms are: • fever (high temperature) and skin rash. Other common symptoms are: • nausea (feeling sick), vomiting (being sick), diarrhoea, abdominal (stomach) pain, severe tiredness. Other symptoms include: • pains in the joints or muscles, swelling of the neck, shortness of breath, sore throat, cough, headache occasionally, inflammation of the eye (conjunctivitis), mouth ulcers, low blood pressure, tingling or numbness of the hands or feet If you continue to take abacavir/lamivudine, the symptoms will get worse, and may be life-threatening. Hypersensitivity reactions can start at any time during treatment with abacavir/ lamivudine, but are more likely during the first 6 weeks of treatment. Occasionally, reactions have developed in people who start taking abacavir again, and had only one symptom on the Alert Card before they stopped taking it. Very rarely, reactions have developed in people who start taking abacavir again, but who had no symptoms before they stopped taking it.	or abdominal pain - severe tiredness or achiness, or generally feeling ill. Your doctor may advise you to stop taking abacavir/lamivudine. The abacavir/lamivudine pack includes an Alert Card, to remind you and medical staff about hypersensitivity reactions. Detach this card and keep it with you at all times If you have stopped taking abacavir/lamivudine because of a hypersensitivity reaction, you must **NEVER AGAIN** take abacavir/lamivudine, or any other medicine containing abacavir. If you do, within hours, your blood pressure could fall dangerously low, which could result in death. If you have stopped taking abacavir/lamivudine for any reason — especially because you think you are having side effects, or because you have other illness: - Talk to your doctor before you start again. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been, you will then be told never again to take abacavir/lamivudine, or any other medicine containing abacavir. It is important that you follow this advice. If your doctor advises that you can start taking abacavir/ lamivudine again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it. If you are hypersensitive to abacavir/lamivudine, return all your unused tablets for safe disposal. Ask your doctor or pharmacist for advice.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in patients with liver disease (Use in subjects with hepatic impairment)	Do not take abacavir/lamivudine if you have severe liver disease. If you have mild or moderate liver disease, taking abacavir/lamivudine is not recommended unless your doctor decides it is necessary. In that case, close monitoring is required. Take special care with abacavir/lamivudine if you have ever had liver disease, including hepatitis B or C (if you have hepatitis B infection, don't stop abacavir/lamivudine without your doctor's advice, as you hepatitis may come back. Talk to your doctor if you have liver disease. Tell your doctor if you have ever had liver disease, including hepatitis B or C. You may need extra check-ups, including blood tests, while you're taking your medicine
Shorter time to HIV becoming resistant to abacavir/lamivudine (Shorter time to virological failure)	The risk of virological failure with the combination of abacavir and lamivudine might be higher than with other therapeutic options
Possible interaction with tenofovir disoproxil fumarate	Tenofovir disoproxil fumarate is a drug used for treating HIV and hepatitis B infections. There have been reports of a high rate of virological failure (HIV becomes resistant to abacavir/lamivudine), and of emergence of resistance at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil fumarate as a once daily regimen. Tell your doctor or pharmacist if you're taking, have recently taken or might take any other medicines.
Carcinogenicity (ability to cause tumours) and long term exposure to abacavir/lamivudine and similar medication	The carcinogenic potential (potential to cause tumours) of a combination of abacavir and lamivudine has not been tested. When studied in rats and mice, lamivudine did not show any carcinogenic potential. Studies with abacavir in mice and rats showed that of some types malignant and non-malignant tumours occurred more in rats and mice. While the relevance of these findings to humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.
Use in 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.
Risk of heart attack (Ischaemic cardiac events)	It cannot be excluded that abacavir may increase the risk of having a heart attack. Tell your doctor if you have heart problems, if you smoke, or have other illnesses that may increase your risk of heart disease such as high blood pressure, or diabetes. Don't stop taking abacavir/lamivudine unless your doctor advises you to do so.

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."

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Allergic reaction to abacavir (ABC hypersensitivity reaction)

Patient Alert Card
Objective and rationale
Allergic reaction to abacavir can be severe and serious. Because of that, it is considered necessary that the risk of allergic reaction to abacavir should be emphasized to patients.
Proposed action: • Inclusion of an alert card in the package of Abacavir/Lamivudine 600 mg/300 mg film-coated tablets to raise the patient's awareness of this risk. • The alert card highlights the risk of a serious allergic reaction when taking this medication, describes possible symptoms to more easily recognize an allergic reaction, gives instructions to contact a doctor immediately if any of the described signs of an allergic reaction occur, and never to restart therapy again.

Education materials for healthcare professionals
Objective and rationale
Increased understanding and awareness of allergic reaction to abacavir by healthcare professionals
Proposed action: • Provision of ABC HSR education materials for healthcare professionals to countries where the MAH is marketing abacavir/lamivudine.

VI.2.6 Planned post authorisation development plan

Study / activity	**Objectives**	**Safety concerns addressed**	**Status**	**Planned date for submission of (interim and) final results**
Antiretroviral pregnancy registry (APR)	Objective of the APR is to detect any major teratogenic effect involving any of the Registry drugs when administered to pregnant women	Use in pregnancy	In progress	Regular APR reports. Estimated study completion date- January 2099

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation

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

Version	Date	Safety Concerns	Comment
1.4	25 Jan 2016	Identified Risks: • Abacavir hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) • Use in subjects with hepatic impairment Potential Risks: • Possible interaction with Ribavirin • Shorter time to virological failure • Possible interaction with Tenofovir Disoproxil Fumarate • Carcinogenicity and long term exposure to NRTIs • Use in pregnancy • Ischaemic cardiac events Missing information: None	RMP v1.4 approved in DE/H/4344/001/DC, on 25-01-2016.
1.5	15 March 2016	No changes in safety concerns or risk minimization measures	Update of RMP for procedure DE/H/4343/001/DC based on updated SPC and PIL. RMP 1.5 approved on 29-04-2016 for DE/H/4343/001/DC.
2.0	30 March 2017	Important identified risks: • Abacavir hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) • Use in subjects with hepatic impairment Important potential risks: • Shorter time to virological failure • Possible interaction with Tenofovir Disoproxil Fumarate • Carcinogenicity and long term exposure to NRTIs • Use in pregnancy • Ischaemic cardiac events Missing information:	Based on a variation following a work-sharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for abacavir/lamivudine originator (Kivexa), the safety concern 'Possible interaction of ABC with ribavirin' was removed from the list of safety concerns.

Version	Date	Safety Concerns	Comment
		• None	
2.1	August 2017	Important identified risks: • Abacavir hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) Important potential risks: • Use in subjects with hepatic impairment • Shorter time to virological failure • Possible interaction with Tenofovir Disoproxil Fumarate • Carcinogenicity and long term exposure to NRTIs • Use in pregnancy • Ischaemic cardiac events Missing information: • None	In line with the reference product, the safety concern 'Use in subjects with hepatic impairment' is considered an important potential risk instead of an important identified risk.