VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

HIV infection

In this decade, the global prevalence of HIV infection stabilized at 0.8%. However, the overall number of people living with HIV increased as new infections continued to occur and AIDS deaths were prevented by increasingly available highly effective antiretroviral treatment (ART). Globally, there were an estimated 33.2 million people living with HIV infection or AIDS in 2007, an increase from 29.5 million in 2001. The annual incidence of new HIV infections declined from an estimated 3.0 million in 2001 to an estimated 2.7 million in 2007. There were an estimated 2.0 million HIV-related deaths in 2007. This number represents an in- crease from 1.7 million deaths in 2001, but as access to treatment increased in this decade, the annual numbers of deaths peaked in 2005 and subsequently decreased. From 2002 to 2007, the number of people receiving ART in developing countries increased from 300 000 to 3.0 million, which was 31% of those who needed treatment.[1]

Heterosexual spread in the general population is the main mode of transmission in sub-Saharan Africa, which remains the most heavily affected region, with 67% of the global burden. Male–male sex, injection drug use, and sex work are the predominant risk factors in most other regions. Infection rates are declining in some regions, including some of the most heavily affected countries in Africa, but climbing elsewhere such as in eastern Europe and central Asia.[1]

VI.2.2 Summary of treatment benefits

HIV infection

The treatment of human immunodeficiency virus (HIV) disease depends on the stage of the disease and any concomitant opportunistic infections. In general, the goal of treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely.[2]

Abacavir/lamivudine is used with other HIV medications to help control HIV infection. It helps to decrease the amount of HIV in the body so that the immune system can work better. This lowers the chance of getting HIV complications (such as new infections, cancer) and improves the quality of life. Abacavir and lamivudine both belong to a class of drugs known as nucleoside reverse transcriptase inhibitors (NRTIs).

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serious allergic reactions in relation to abacavir [ABC hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing)]	This medicinal product contains abacavir (which is also an active ingredient in other related medicines). Some people who take abacavir may develop a hypersensitivity reaction (a serious allergic reaction), which can be life-threatening if they continue to take abacavir. 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 hypersensitivity reaction (a serious allergic reaction). Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome. Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough, and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, and arthralgia). Symptoms related to this hypersensitivity reaction worsen with continued therapy	Patients must not take this medicinal product if they are allergic (hypersensitive) to abacavir (or any other medicine containing abacavir), lamivudine or any of the other ingredients of this medicine. Patients must carefully read all the information about hypersensitivity reactions in Section 4 of the Package Leaflet. If patients have stopped taking abacavir/lamivudine for any reason — especially because they think they are having side effects, or because they have other illness: o Patients must talk to their doctor before they start taking it again. Doctor will check whether symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been related, patients will be told never again to take this medicinal product, or any other medicine containing abacavir. It is important that patients follow this advice. Patients must contact their doctor immediately: 1. if they get a skin rash, OR 2. if they get symptoms from at least 2 of the following groups: o fever o shortness of breath, sore throat or cough o nausea or vomiting, diarrhoea or abdominal pain o severe tiredness or achiness, or generally feeling

Risk	What is known	Preventability
	and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir. □ 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, especially during the first two months of treatment with abacavir, with consultation every two weeks. □ 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 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 minimise the risk of a life-threatening hypersensitivity reaction, abacavir/lamivudine 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 medicinal products). □ Special care is needed for those patients simultaneously starting treatment with abacavir/lamivudine and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is currently	ill. □ Doctor may advise patients to stop taking this medicinal product. □ The product's pack includes an Alert Card, to remind patients and medical staff about abacavir hypersensitivity. This card must be detached and kept by patients at all times. □ The Alert Card enclosed within this product contains important safety information. □ If patients have stopped taking this medicinal product because of a hypersensitivity reaction, they must NEVER AGAIN take this or any other medicine containing abacavir. If they do, within hours, blood pressure could fall dangerously low, which could result in death. □ If doctor advises that patients can start taking this product again, they may be asked to take their first doses in a place where they will have ready access to medical care if they need it. □ If patients are hypersensitive to this product, they must return all unused abacavir/lamivudine tablets for safe disposal. Patients must seek their doctor's or pharmacist's advice.

Risk	What is known	Preventability
	difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.	
Use in subjects with hepatic impairment	□ The safety and efficacy of abacavir/lamivudine has not been established in patients with significant underlying liver disorders. □ Abacavir/lamivudine is contraindicated in patients with severe hepatic impairment. □ 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. □ Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. □ Liver disorders, such as jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems), enlarged liver or fatty liver, inflammation (hepatitis) is a rare side effect (it may affect up to 1 in 1000 people).	□ Patients having severe liver disease must not take this medicinal product. □ Some people taking abacavir/lamivudine or other combination treatments for HIV are more at risk of serious side effects. Patients need to be aware of the extra risks: o if they had previously liver disease, including hepatitis B or C (if they have hepatitis B infection, abacavir/lamivudine must not be stopped without doctor's advice, as hepatitis may come back).

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Long term risk of carcinogenicity and long term exposure to NRTIs	The active ingredients of abacavir/lamivudine may inhibit cellular DNA replication and abacavir has been shown to be carcinogenic in animal models. The clinical relevance of these findings is unknown. Placental transfer of abacavir and lamivudine has been shown to occur in humans. The carcinogenic potential of a combination of abacavir and lamivudine has not been tested. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show

Risk	What is known (Including reason why it is considered a potential risk)
	any carcinogenic potential. Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.
Use in pregnancy	Abacavir/lamivudine is not recommended for use during pregnancy. Abacavir/lamivudine and similar medicines may cause side effects in unborn babies. In case of pregnancy while taking abacavir/lamivudine, the baby may be given extra check-ups (including blood tests) to make sure it is developing normally. Patients must consult their doctor immediately about the risks and benefits of taking abacavir/lamivudine, or other medicines for treating HIV infection, during pregnancy.
Ischaemic cardiac events	Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing abacavir/lamivudine, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).
Possible interaction of ABC with ribavirin	Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. As abacavir and ribavirin share the same phosphorylation pathways, a possible intracellular interaction between these drugs has been postulated, which could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a possible consequence, a reduced chance of sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus RBV. Conflicting clinical findings are reported in literature on co-administration between abacavir and ribavirin. Some data suggest that HIV/HCV co-infected patients receiving abacavir-containing ART may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both drugs are co-administered.
Possible interaction of ABC/3TC with tenofovir disoproxil fumarate	- Triple nucleoside therapy: There have been reports of a high rate of virological failure, and of emergence of resistance at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil fumarate as a once daily regimen. - The risk of virological failure with abacavir/lamivudine might be higher than with other therapeutic options.
Risk of shorter time to viro-	- Triple nucleoside therapy: There have been reports of a

Risk	What is known (Including reason why it is considered a potential risk)
logical failure	high rate of virological failure, and of emergence of resistance at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil fumarate as a once daily regimen. - The risk of virological failure with abacavir/lamivudine might be higher than with other therapeutic options.

Missing information

Risk	What is known
NA	NA

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:

Serious allergic reactions in relation to abacavir [ABC hypersensitivity reaction (in- cluding reduced vigilance following HLA-B*-5701 testing)]

Healthcare Professional and patient education
Objective and rationale: To increase HCP awareness of the risk of hypersensitivity reaction and to provide guidance about patients at special risk and on how to manage it. Patients will also receive an alert card summarising key safety information on hypersensitivity reactions with this medicine in order to ensure prompt recognition of possible hypersensitivity symptoms.
Proposed action: - Provision of an ABC HSR education material for healthcare professionals in the form of a *Prescriber brochure* including information regarding: • Major symptoms associated with ABC HSR • Risk factors for ABC HSR • Recommendations for HLA-B*5701 screening • Information on HLA-B B*5701 testing • Management of ABC HSR reaction • Hypersensitivity case studies -*Patient Alert Card* to be included in each pack and kept by the patients in order to remind them about possible symptoms of abacavir hypersensitivity and the need to contact the doctor if they occur.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for abacavir/lamivudine.

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

Version	Date	Safety Concerns	Comment
1.0	03-04-2015	**Identified Risks** -ABC hypersensitivity reaction (including reduced vigilance following HLA-B*-5701 testing) -Use in subjects with hepatic impairment **Potential Risks** -Long term risk of carcinogenicity and long term exposure to NRTIs -Use in pregnancy -Ischaemic cardiac events -Possible interaction of ABC with ribavirin -Possible interaction of ABC/3TC with tenofovir disoproxil fumarate -Risk of shorter time to virological failure **Missing information** NA	First version
1.1	06-10-2015	No changes	Brand name changed