VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology1

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. There are nearly 110,000 people living with HIV in the UK. 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 antiviral medicine 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 the 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.

VI 2.3 Unknowns relating to treatment benefits

Lamivudine (3TC) was approved for use in 1996 for the treatment of HIV in combination with other antiretroviral agents and ABC was approved in Europe in 1999 (and have a well-established safety profile in a wide range of subjects).

However, in the clinical trials conducted before ABC/3TC were approved, some people were not allowed to take part. This was because of problems that could affect how well the drug works; however, in some cases, ABC/3TC may be prescribed to such patients, especially where other conditions or illnesses can also be carefully managed and monitored. The groups of people not included in the ABC/3TC studies were:

- People whose alcohol or illegal drug use might make them less likely to follow treatment directions
- People who had problems of digestion (such as not absorbing nutrition well) that could interfere with treatment

- People who had inflammation of the pancreas or liver in the 6 months before the study
- People with poor kidney function
- People with some types of abnormal blood levels, including haemoglobin, neutrophils, or platelets
- People with abnormal levels of liver or pancreas enzymes
- People with other serious illnesses such as diabetes or heart conditions.

ABC/3TC was also not studied in people who were taking certain other medicines, such as for treating cancer, as it was not known at the time if it was safe to do so. However, in the real life setting ABC/3TC may be prescribed with some of these medicines.

ABC has been studied in people with mild liver disease, but not in people with moderate or severe liver disease. If ABC/3TC is used in patients with mild or moderate liver disease, it is recommended that blood levels of ABC are monitored if possible.

In the main studies of ABC/3TC in adults, women who were pregnant or breast feeding an infant could not take part. There has been a small study in pregnant women.

In the main studies of ABC/3TC, most people taking part were Caucasian men. A more recent study included half women and also a large percentage of other races such as blacks. This study did not show differences in response to ABC between men and women or between different races.

A limited number of people older than 65 years took part in the studies of ABC/3TC.No studies were formally carried out in children taking ABC/3TC. Therefore, ABC/3TC is not recommended to be used in children weighing less than 25 kg.

VI 2.4 Summary of safety concerns

Table 22 Part VI - Summary table 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 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	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. 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.

Risk	What is known	Preventability
	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.	

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. 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.
Ischaemic cardiac events (risk of heart attack and other effects of blood supply to the heart muscle).	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

Risk	What is known (Including reason why it is considered a potential risk)
	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.
Shorter time until ABC/3TC becomes ineffective as HIV treatment (Risk of shorter time to virological failure)	Patients taking ABC/3TC 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 become resistant to ABC/3TC.
Use in pregnancy and breastfeeding (Use in pregnancy and lactation)	Abacavir/lamivudine film coated tablets is not recommended for use during pregnancy. Abacavir/lamivudine and similar medicines may cause side effects in unborn babies. ~~There is no information on the safety of Abacavir sulfate and Lamivudine when used during pregnancy.~~ Studies in animals have shown that Abacavir/lamivudine crosses the placenta and may have harmful effects when used 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

Risk	What is known (Including reason why it is considered a potential risk)
	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. Women who are HIV-positive must not breast-feed, because HIV infection can be passed on to the baby in breast milk. The ingredients found in Abacavir/lamivudine can also pass into the breastmilk.
Drug interaction with ribavirin	Abacavir may make ribavirin less effective at reducing levels of hepatitis C virus (a type liver problem) in the body.
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.
Risk of cancer in patients who take HIV drugs such as ABC for a long time (Carcinogenicity and long term use)	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.

VI 2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. The measures in these documents are known as routine risk minimisation measures. This product has additional risk minimisation measures.

Additional risk minimisation are described below:

Abacavir hypersensitivitiy reaction (HSR)

Additional risk minimisation measures: Healthcare Professional in the form of slide set and patient alert card

Objective and rationale:

- To increased understanding and awareness of abacavir HSR.
- To prevent occurrence of abacavir HSR in patients treated with abacavir/lamivudine by screening the patients for HLA-B*5701 allele before initiating treatment with products containing abacavir.
- 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 abacavir HSR and re-challenge to abacavir.
- To detect any possible new features of HSR, or changing trends in circumstances around HSR (e.g., incidence and reasons for re-challenge).

Proposed action:

For patients being treated with Abacavir/lamivudine: provision of alert card for abacavir hypersensitivity reaction included with the product in each packaging.

For HCPs: Provision of education materials to HCPs (in the form of a slide set) in countries where the MAH has marketing authorisation, before launching the product on the respective market. The educational materials will cover the following key elements:

- Major symptoms associated with ABC HSR
- Pharmacogenetic testing (HLA-B*5701 testing)

Abacavir hypersensitivitiy reaction (HSR)

- Management of ABC HSR reaction
- Hypersensitivity case studies

The educational materials and will be reviewed annually. The effectiveness of the additional risk minimisation measure shall be done assessed by conducting an annual review of all reported HSR cases in the member states in which the product is marketed and the criteria for judging the success of the proposed risk minimisation measures will be by monitoring via an annual

review of all reported HSR cases in the member states in which the product is marketed. The review shall focus on:

- the annual incidence of all HSR cases from clinical trials and the annual reporting rate of spontaneous cases.
- The country of origin, case type, time to onset and seriousness of all cases in the period.
- Severity of cases by review of reporting rate and analysis of life threatening and fatal cases.
- Failure of risk minimisation through review of HSR occurring in patients reported not to have been tested for the HLA-B5701 gene.
- Review of HSR occurring in patients reported to have tested positive for the HLA-B5701 marker gene prior to starting ABC treatment

- Analysis of ABC rechallenge cases.

VI 2.6 Planned post authorisation development plan

No studies planned.

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

Not applicable.