RISK MANAGEMENT PLAN

FOR

LAMIVUDINE / ZIDOVUDINE

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Human Immunodeficiency Virus (HIV) infection

HIV stands for human immunodeficiency virus. It kills or damages the body's immune system cells. AIDS stands for acquired immunodeficiency syndrome. It is the most advanced stage of infection with HIV. HIV most often spreads through unprotected sex with an infected person. It may also spread by sharing drug needles or through contact with the blood of an infected person.

In United Kingdom (UK), HIV infection & AIDS estimation for 2013 showed Number of people living with HIV was 130000; Adults aged 15 to 49 occurrence rate is 0.3 %; Adults aged 15 and up living with HIV was 130000; Women aged 15 and up living with HIV was 38000; Deaths due to AIDS were <1000; Number of new infection all ages was 6800; Children aged 0 to 14 living with HIV and Orphans due to AIDS aged 0 to 17 are not applicable.

There is no cure for HIV, but early detection and effective treatment with medicines that stop the virus multiplying and allowing patients to stay healthy and live longer lives.

VI.2.2 Summary of treatment benefits

In clinical studies, subjects receiving lamivudine and zidovudine with or without additional concomitant antiretroviral therapies and who already present with the M184V mutant virus also experience a delay in the onset of change in a DNA sequence that confer resistance to zidovudine and stavudine. Also lamivudine in combination with zidovudine has been shown to reduce human immunodeficiency virus load with no prior antiretroviral therapy with increasing CD4 cell count, results in a reduce the spread of disease and death.Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the M184V mutations.

VI.2.3 Unknowns relating to treatment benefits

No specific data are available for use of Lamivudine / Zidovudine in elderly patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Abnormally low neutrophil counts, abnormally low haemoglobin levels and abnormally low white blood cells level (Haematological adverse reactions)	When people take a Lamivudine / Zidovudine, their blood tests shown common side effects: a low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia*or *leucopenia*) these may affect up to 1 in 10 people and also very rare side effect: a failure of the bone marrow to produce new red or white blood cells (*aplastic anaemia*) these may affect up to 1 in 10,000 people.	Yes. Do not take Lamivudine / Zidovudine if you have a very low haemoglobin (*anaemia*) or a very low white blood cell count (*neutropenia*). Doctor should check your haemoglobin,red blood cell count or a white blood cell count before giving a Lamivudine / Zidovudine.
Old infections may flare up (Opportunistic infections)	People with advanced human immunodeficiency virus (HIV) infection have weak immune systems, and are more likely to develop serious infections	Yes. If you get any symptoms of infection while you're taking Lamivudine / zidovudine tell your doctor immediately. Do not take other medicines for

Risk	What is known	Preventability
	(opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.	the infection without your doctor's advice. if you have hepatitis B infection, don't stop Lamivudine / zidovudine without your doctor's advice, as your hepatitis may come back
Lacticacidosis (lactic acid accumulates in the bloodstream)	If people take Lamivudine / Zidovudine, a rare side effect like lactic acidisis may affect up to 1 in 1000 people. Some people taking Lamivudine / zidovudine, or other medicines like it nucleoside reverse transcriptase inhibitors (NRTIs) develop a condition called lactic acidosis, together with an enlarged liver.	Yes During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms likes deep, rapid, difficult breathing, drowsiness, numbness or weakness in the limbs, feeling sick (nausea), being sick (vomiting), stomach pain or any other symptoms that worry you see your doctor as soon as possible.

Risk	What is known	Preventability
	Lactic acidosis is caused by a build up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs. Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women. **Signs of lactic acidosis include:** • deep, rapid, difficult breathing • drowsiness • numbness or weakness in the limbs • feeling sick (nausea), being sick (vomiting) • stomach pain. Combination therapy for human immunodeficiency virus (HIV) can also cause increased levels of lactic	

Risk	What is known	Preventability
	acid in the blood may show up in blood tests, which on rare occasions can lead to lactic acidosis.	
Redistribution of body fat (Lipoatrophy)	People taking combination therapy for human immunodeficiency virus (HIV) may find that their body shape changes, because of changes in fat distribution: • fat may be lost from the legs, arms or face. • extra fat may build up around the tummy (abdomen), or on the breasts or internal organs. • fatty lumps (sometimes called buffalo hump) may appear on the back of the neck. It is not yet known what causes these changes, or whether they have any long-term effects on your health.	Yes. If you notice changes in your body shape tell your doctor.

Risk	What is known	Preventability
	When people taking combination therapy your blood tests show up an increased levels of sugar and fats (triglycerides and cholesterol) in your blood.	
A condition that occurs when the immune system attacks healthy body tissue (Immune Reactivation Syndrome)	If people start taking lamivudine / zidovudine, they had opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may occur. Autoimmune disorders may occur many months after the start of treatment and immediately to seek necessary treatment.	Yes, If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor. Do not take other medicines for the infection without your doctor's advice.
Parts of the bone tissue die because of reduced blood supply to the bone. (Osteonecrosis)	If you take Lamivudine / Zidovudine, you suffer from osteonecrosis (parts of the bone tissue die because of reduced blood supply to the bone). Osteonecrosis may occur in following conditions:	Yes, If you notice stiffness in the joints, aches and pains (especially in the hip, knee or shoulder) and difficulty moving tell your doctor immediately.

Risk	What is known	Preventability
	• if you have been taking combination therapy for a long time • if you are also taking anti-inflammatory medicines called corticosteroids • if you drink alcohol • if your immune systems are very weak and • if you are overweight. **Signs of osteonecrosis include:** • stiffness in the joints • aches and pains (especially in the hip, knee or shoulder) • difficulty moving.	
Liver disorders (Hepatic adverse events)	Please do not take Lamivudine / Zidovudine, if you have ever had liver disease, including hepatitis B or C. When u take Lamivudine / Zidovudine, an increase in the level of liver enzymes	Yes, If you have hepatitis B infection, don't stop Lamivudine / zidovudine without your doctor's advice, as your hepatitis may come back. Medicinal products containing

Risk	What is known	Preventability
	and *bilirubin* (a substance produced in the liver) show up in blood tests. People also suffer from liver disorders, such as jaundice, enlarged liver or fatty liver, inflammation (*hepatitis*) while receiving Lamivudine / Zidovudine may affect up to 1 in 1000 people.	lamivudine, to treat HIV infection or hepatitis B infection not be used with Lamivudine / zidovudine
Tiredness, lack of energy (Mitochondrial dysfunction)	Mitochondrial dysfunction: nucleoside and nucleotide analogues of Lamivudine / Zidovudine have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. If people take Lamivudine / Zidovudine, a common side effect like tiredness, lack of energy may affect up to 1 in	Yes, If you notice tiredness, lack of energy, please immediately inform to your doctor.

Risk	What is known	Preventability
	1000 people.	

Important potential risks

Risk	What is known
Inflammation of the pancreas,which is large gland behind the stomach which secretes digestive juices and hormones (Pancreatitis)	If people take Lamivudine / Zidovudine, a rare side effect like inflammation of the pancreas (*pancreatitis*) may affect up to 1 in 1000 people. If people take Lamivudine / Zidovudine rises in serum amylase (one type of enzyme produced by pancreas) may occur rarely.
Interaction of lamivudine with cladribine	Cladribine (anti cancer drug use to treat one type of blood cancer) should not be used with Lamivudine / zidovudine, due to this combination effect of cladribine may decrease. Tell your doctor if you are being treated with Cladribine while receiving Lamivudine / zidovudine.
Interaction of zidovudine with stavudine(anti HIV drug)	Stavudine should not be used with Lamivudine / zidovudine because decreased efficacy of both drugs. Tell your doctor if you are being treated with stavudine while receiving Lamivudine / zidovudine.
Over exposure of zidovudine in paediatric patients weighing 14-30 kg.	In paediatric patients weighing 14-30 kg, higher exposure of zidovudine can occur; therefore dosage should be closely monitoredin these patients.
Risk of choking associated with tablets in younger	The tablet(s) should ideally be swallowed without crushing.

Risk	What is known
children	For patients who are unable to swallow tablets, tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Missing information

Risk	What is known
Use in elderly patient	Special care is advised in elderly patient due to age associated changes such as the reduced in kidney function and alteration of neutrophil levels, haemoglobin levels and white blood cells level.
A substance which increase a risk of cancer [Carcinogenic Potential (Carcinogenicity)]	The cancer causing risk of a combination of lamivudine and zidovudine has not been tested. However, Animal studies have shown that zidovudine cause cancer in fetus and vaginal (female genital organ) tumours were the result of long term use. In addition, one animal study showed zidovudine given at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring.

Risk	**What is known**
Natural capability to produce offspring (Fertility)	There are no data on the affect of drug on human female fertility. In Animal studies neither zidovudine nor lamivudine have shown evidence of impairment of natural capability to produce offspring in male and female rats. In men zidovudine has not been shown to affect seed (sperm) count, structure of cell (organisms) or ability to move.
Induction of permanent transmissible changes in the structure of the genetic material of cells or organisms (Mutagenicity) 1	Neither lamivudine nor zidovudine is changes the genetic material of cells or organisms in germ (bacterial) tests.
The toxic effects of a substance on the new individual organisms "offspring" are produced from their "parents" and the development of offspring. (Reproductive toxicity)	Animal studies shown lamivudine causing an increase in early embryonic deaths in the rabbit at relatively low dose, comparable to dose used in man, but not in the rat even at very high dose. Zidovudine had a similar effect in both species, but only at very high doses. Animal studies have shown, Lamivudine was not disturbing the development of an embryo or fetus. At toxic doses of mother, zidovudine given to rats during development of internal organs of the organism resulted in abnormally formed part of the body but no evidence of such abnormality was observed at lower doses.

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 minimizing 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 no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned

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

Version	Date	Safety Concern	Comment
2.0	18-Nov-2016	Safety concern "Lipodistrophy" has been updated to "Lipoatrophy"	In the RMP, the safety concern "Lipodistrophy" has been adapted to "Lipoatrophy" taking in account the latest updated advice on body fat changes and lactic acidosis with HIV medicines, dated 23 October 2015 (EMA/688896/2015) RMP has been revised as per updated SPC and PL