Summary of Product Characteristics Lazidariv Paediatric Film Coated Tablets (Lamivudine (3TC) and Zidovudine (AZT) Tablets USP 30:60 mg)

1. **Name of the Medicinal Product**
   Lazidariv Paediatric Film Coated Tablets

2. **Qualitative and Quantitative Composition**
   Each film-coated tablet contains 30 mg Lamivudine and 60 mg Zidovudine.

3. **Pharmaceutical Form**
   Film Coated Tablet

4. **Clinical Particulars**

4.1 Therapeutic Indications

The fixed combination of Lamivudine and Zidovudine is indicated in combination with another antiretroviral agent for the treatment of Human Immunodeficiency Virus (HIV) infection in children.

4.2 Posology and Method of administration

Oral use.
Therapy should be prescribed by a physician experienced in the management of HIV infection.

Children 6 weeks of age and above:
Number of tablets by weight band to be taken twice daily (approximately 12 hours apart)

Number of tablets by weight band (twice daily)				
3-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg
1	1.5+	2	2.5*	3

+ This dose can either be delivered as one and a half tablets twice daily or by giving 2 tablets in the morning and 1 tablet in the evening.
* This dose can either be delivered as two and a half tablets twice daily or by giving 3 tablets in the morning and 2 tablets in the evening.

Children weighing 25 kg or more, adolescents and adults:
For these patient groups other fixed dose formulations with higher amounts of the active substances are available.

Lamivudine/Zidovudine 30mg/60mg Tablets can be taken with or without food.

4.3 Contraindications

Lamivudine/Zidovudine 30mg/60mg Tablets is contraindicated in patients

- With hypersensitivity to lamivudine, zidovudine or to any of the excipients contained in the formulation
- With abnormally low neutrophil counts (< 0.75 x 10 9 /l).
- With abnormally low haemoglobin levels (< 7.5 g/dl or 4.65 mmol/l).

4.4 Special warnings and precautions for use

Lamivudine/zidovudine should only be used in combination with abacavir in the treatment of antiretroviral therapy (ART) naïve patients when a regimen based on a protease inhibitor (PI) or a nonnucleoside inhibitor of reverse transcriptase (NNRTI) cannot be used.

Dose adjustments: It is recommended that separate preparations of lamivudine and zidovudine be administered when any dosage adjustment is necessary. In these cases the health care provider should refer to the individual prescribing information for these medicinal products.

Opportunistic infections: Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

Transmission of HIV: Treatment with Lamivudine/Zidovudine 30mg/60mg Tablets has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Haematological adverse reactions: Anaemia, neutropenia and leucopenia have been reported in patients receiving zidovudine-containing preparations, especially in patients with advanced HIV disease (poor bone marrow reserve) or low serum vitamin B12 levels, and usually after at least 4-6 weeks of therapy.

Pancreatitis: Treatment with Lamivudine/Zidovudine 30mg/60mg Tablets should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis: Lactic acidosis is a rare but severe, potentially life-threatening complication associated with NRTI use. It may occur after a few to several months of treatment.

Mitochondrial dysfunction: Nucleoside and nucleotide analogues 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 postnatally to nucleoside analogues. The main

adverse events reported are haematological disorders (anaemia and neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of ART and related metabolic disturbances.

Immune Reactivation Syndrome: In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

Liver disease: Caution should be exercised when administering Lamivudine/Zidovudine 30mg/60mg Tablets to any patient with chronic hepatitis B infection.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in (adult) patients with advanced HIV-disease and/or long-term exposure to combination ART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine/Zidovudine 30mg/60mg Tablets contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with Lamivudine/Zidovudine 30mg/60mg Tablets.

Interactions relevant to lamivudine:
Because of overlapping resistance and lack of additive antiretroviral effects, lamivudine should not be co-administered with emtricitabine.
Co-administration with trimethoprim / sulfamethoxazole results in a 40% increase in lamivudine exposure because of the trimethoprim component. Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary.
Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. Lamivudine does not inhibit the cytochrome P450 isoform CYP3A.

Interactions relevant to zidovudine:
Since zidovudine and stavudine act antagonistic in vitro, Lamivudine/Zidovudine 30mg/60mg Tablets should not be used concomitantly with stavudine. Co-administration of zidovudine with ribavirin leads to additive or synergistic bone marrow toxicity. For this reason, zidovudine should be replaced by an alternative antiretroviral agent in patients treated with ribavirin.
Co-administration of zidovudine with rifampicin decreases the exposure to zidovudine. However, the clinical significance of this is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.
Probenecid, valproic acid and fluconazole increase the exposure to zidovudine. Patients should be closely monitored for haematological toxicity.
Clarithromycin tablets reduce the absorption of zidovudine. The clinical relevance is unclear. However, this effect can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.
Atovaquone and methadone have been shown to increase exposure to zidovudine.
The clinical relevance is unknown. Phenytoin plasma levels have been reported to be altered in either way in patients receiving zidovudine. Thus, phenytoin levels should be careful monitored in patients receiving Lamivudine/Zidovudine 30mg/60mg Tablets and phenytoin.

4.6 Pregnancy and lactation

Pregnancy: No increased risk of birth defects has been reported for lamivudine or zidovudine. However, risks to the fetus cannot be ruled out.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Lamivudine/Zidovudine 30mg/60mg Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable Effects

As Lamivudine/Zidovudine 30mg/60mg Tablets contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following the concurrent administration of the two agents. The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia.

Adverse events considered to be at least possibly related to treatment with zidovudine and lamivudine, are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000) or very rare (≤ 1/10,000).

In addition, adverse events identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine as a fixed-dose combination are listed (frequency category: 'unknown'). Since they were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, number of reports, or potential causal connection to lamivudine, zidovudine, and/or lamivudine / zidovudine as fixed-dose combination.

Blood and lymphatic systems disorders
Common: Anaemia, neutropenia, leucopenia,
Uncommon: Thrombocytopenia, pancytopenia
Rare: Pure red cell aplasia
Very rare: Aplastic anaemia.

Metabolic and nutrition disorders
Rare: Lactic acidosis
Unknown: changes in distribution of body fat, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia

Psychiatric disorders
Rare: anxiety, depression.

Nervous system disorders
Very common: Headache Common: Dizziness, insomnia
Rare: Paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders
Rare: Cardiomyopathy.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Rare: cough.

Gastrointestinal disorders
Very common: Nausea Common: Vomiting, abdominal pain and diarrhoea
Uncommon: Flatulence
Rare: Pancreatitis, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders
Common: Elevated liver enzymes and bilirubin
Rare: Hepatitis, severe hepatomegaly with steatosis.

Skin and subcutaneous tissue disorders
Common: Rash, hair loss
Uncommon: Pruritus

Rare: Nail and skin pigmentation, urticaria, sweating.

Musculoskeletal and connective tissue disorders
Common: Myalgia
Uncommon: Myopathy, osteonecrosis

Renal and urinary disorders
Rare: Urinary frequency.

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site disorders:
Common: Malaise, fatigue
Uncommon: Asthenia, fever, generalized pain
Rare: Chest pain, influenza-like syndrome, chills
Unknown: Immune reconstitution syndrome

5 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. If overdose occurs patients should be monitored for toxicity, and standard supportive treatment applied as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage.

6 Pharmacological Properties

6.1 Pharmacodynamic Properties

Lamivudine and zidovudine are nucleoside analogues that have activity against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolised intracellularly to their active moieties, lamivudine 5'- triphosphate (TP) and zidovudine 5'-triphosphate respectively. Their main modes of action are as chain terminators of viral reverse transcription.
Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

6.2 Pharmacokinetic Properties

Absorption
Lamivudine and zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80

– 85% and for zidovudine 60 – 70%. Following single dose administration of Lamivudine/Zidovudine 30mg/60mg Tablets in healthy volunteers, mean (± SD) of lamivudine and zidovudine Cmax values were 1856 ng/ml (± 633) and 1974 ng/ml (± 961), respectively and the corresponding values for AUC were 6801 ng.h/ml (± 1561) and 2634 ng.h/ml (± 692)respectively. The mean (± SD) lamivudine and zidovudine tmax values were 1.23 hours (± 0.55) and 0.77 hours (± 0.54) respectively.
The extent of lamivudine and zidovudine absorption (AUC) and estimates of half-life following administration of a respective fixed combination product with food were similar when compared to fasting subjects, although the rates of absorption (Cmax, tmax) were slowed. Based on these data Lamivudine/Zidovudine 30mg/60mg Tablets may be administered with or without food.

Distribution
Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6 l/kg respectively.
Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36% serum albumin *in vitro*). Zidovudine plasma protein binding is 34% to 38%. Drug interactions involving binding site displacement are not anticipated with Lamivudine/Zidovudine 30mg/60mg Tablets.

Metabolism
Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared unchanged by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10%) and low plasma protein binding. The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 – 80% of the administered dose eliminated by renal excretion. 3'-amino-3'- deoxythymidine has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination
The observed lamivudine half-life of elimination is 5 to 7 hours. The half-life of intracellular lamivudine triphosphate has been estimated to approximately 22 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70%), including tubular secretion through the organic cationic transport system. Studies in patients with renal impairment show that lamivudine elimination is affected by renal dysfunction. Dose reduction is recommended for patients with creatinine clearance ≤ 50 ml/min.

Special populations:
Pregnancy: The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant women. Children: In general, lamivudine

pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65%) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age, approaching adult values around 12 years of age.
In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels studied in adults and children, the bioavailability was between 60-74%.

6.3 Preclinical safety data

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in *in vitro* mammalian tests such as the mouse lymphoma assay.
The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested.
In oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In reproductive toxicity studies lamivudine has demonstrated evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

7 Pharmaceutical Particulars

7.1 List of Excipients

Microcrystalline Cellulose BP (Dried)
Sodium Starch Glycollate BP
Colloidal Anhydrous Silica BP
Magnesium Stearate BP
Opadry 16B280001
Purified Water BP

7.2 Incompatibilities
None

7.3 Shelf life
2 Years

7.4 Special precautions for storage
Do not store above 30°C. Keep in tightly closed container. Store in original container.

7.5 Nature and contents of container
White Opaque HDPE Container

7.6 Instructions for use, handling and disposal
No special requirements

8 Registrant
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9 Manufacturer
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10 Date of revision of text
19/08/2015

11 Dosimetry (if applicable)
New registration

12 Instructions for Preparation of radiopharmaceuticals (if applicable)
New registration

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