Application for inclusion of a medicine in the WHO Model List of Essential Medicines for Children

1. **Summary statement of the proposal for inclusion:**

The number of people living with HIV increased in every region in the world in the past two years. An estimated 2.3 million children were living with HIV/AIDS at the end of 2006, 2 million of them in sub-Saharan Africa and an estimated 1500 children get newly infected with HIV each day. (UNAIDS/WHO "AIDS Epidemic Update: December 2006". Downloaded from weblink:http://www.unaids.org/en/HIV_data/epi2006/default.asp on 14.05.2007).

Without HIV care, including antiretroviral therapy, the progression of HIV infection in children is particularly aggressive. Antiretroviral therapy has proven to be highly effective in children, including for those in resource-poor settings. Rapid initiation of treatment restores and preserves immune functions, promotes normal growth and development, and prolongs life. Generally, some 80% of children with HIV die by age five years if they do not receive antiretroviral therapy. In high-income countries, where most children with perinatally acquired HIV infection are treated early with antiretroviral therapy, the treatment has been shown to reduce mortality by five-fold or more and results in survival rates of 80% and higher (HIV in children: Taking stock: WHO/HIV/2006.04. Downloaded from weblink: **http://www.who.int/entity/hiv/toronto2006/takingstockchildren.pdf,** on 14.05.2007).

Since antiretroviral therapy needs to be administered for many years, considerations related to the choice of initial antiretroviral regimen include an understanding of barriers to adherence, including the 'pill load', complexity of treatment schedules and food requirements for different regimens, as well as palatability problems and potential limitations in subsequent treatment options should resistance develop. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to demanding treatment regimes in order to prevent emergence of drug-resistant HIV variants that lead to regimen failure and limit options for future therapy (Chesney M, 2003).

Combination therapy is recommended in HIV infection for all infants, children, and adolescents who are treated with antiretroviral agents. Compared with monotherapy, combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used (Guidelines for the use of antiretroviral agents in pediatric HIV infection, Oct 2006. National Institute of Health. http://aidsinfo.nih.gov/).

There is an urgent need for affordable, safe, quality ARV formulations appropriate for paediatric use, particularly solid fixed dose combination (FDC) formulations to facilitate programming planning, improve adherence and facilitate scale up of HIV care for children, in line with a public health approach.

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: protease inhibitor-based (2 NRTIs plus a protease inhibitor); NNRTI-based (2 NRTIs plus an NNRTI); and NRTI based (3 NRTI drugs).

The preferred option when choosing a first-line regimen for infants and children is two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). Lamivudine and stavudine are recommended preferred first-line as the dual NRTI combination in NNRTI based regimens. Nevirapine is recommended NNRTI for children < 3 years of age (Guidelines for the use of antiretroviral agents in paediatric HIV infection, Oct 2006. National Institute of Health. http://aidsinfo.nih.gov/; Antiretroviral therapy of HIV infection in infants and children in resource-limited settings:

towards universal access, Recommendations for a public health approach, World Health Organization 2006).

Ranbaxy Laboratories Limited has developed a fixed dose combination (FDC) tablets for oral suspension containing the antiretroviral drugs lamivudine (NRTI), nevirapine (NNRTI) and stavudine (NRTI) for the treatment of HIV infection in children. The proposed Fixed Dose tablets for oral suspension offers a rationale combination for the treatment of HIV/AIDS patients and is one of the first line NNRTI- based regimens recommended by WHO and National Institute of Health guidelines (Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access, Recommendations for a public health approach, World Health Organization 2006; Guidelines for the use of antiretroviral agents in paediatric HIV infection, Oct, 2006. National Institute of Health. http://aidsinfo.nih.gov/). Two strengths viz lamivudine 40 mg, stavudine 10 mg and nevirapine 70 mg and its half strength tablets have been developed. The FDC would provide the recommended doses of lamivudine, stavudine and nevirapine in paediatric patients weighing between 9-31 Kgs.

The safety and efficacy of Lamivudine, stavudine and nevirapine in the treatment of HIV patients has been established in various clinical trials. Lamivudine, nevirapine and stavudine are generally well tolerated; adverse events are usually mild to moderate and reversible upon discontinuation of treatment.

The proposed FDC would provide cost effective treatment in comparison to the currently available individual liquid formulations of lamivudine, nevirapine and stavudine.

2. Name of the focal point in WHO submitting or supporting the application

Prof. Charlie Gilks
Department of HIV
World Health Organization
Geneva 27
Switzerland

3. Name of the organization(s) consulted and/or supporting the application

World Health Organization.

4. International Non-proprietary Name (INN, generic name) of the medicine

International Non-proprietary Name (INN, generic name) of the individual components of the FDC are given below:

- Lamivudine
- Nevirapine
- Stavudine

5. Dosage form or strength proposed for inclusion

The Ranbaxy`s formulation will be available as tablets for oral suspension. Two strengths viz lamivudine 40 mg, stavudine 10 mg and nevirapine 70 mg and its half strength tablets have been developed. The composition of proposed FDC is presented below:

FDC Components	Triviro LNS kid DS	Triviro LNS kid
Lamivudine	40 mg	20 mg
+	+	+
Stavudine	10 mg	5 mg
+	+	+
Nevirapine	70 mg	35 mg

6. International availability - sources, if possible manufacturers

Manufactured and Marketed by

Ranbaxy Laboratories Limited
Paonta Sahib
District Sirmour
Himachal Pardesh - 173025
India.

International availability

Country	Product Name	Generic Name
India	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension
Nigeria	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension
India	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension
Nigeria	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual Medicine.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Disease Burden:

In 2006, there were 2.3 million (1.7–3.5 million) children living with HIV worldwide, an estimated 3, 80, 000 (2,90,000–5,00,000) children died of HIV-related causes worldwide. The number of people living with HIV increased in every region in the world in the past two years. The most striking increases have occurred in East Asia and in Eastern Europe and Central Asia, where the number of people living with HIV in 2006 was over one fifth (21%) higher

than in 2004 (UNAIDS/WHO "AIDS Epidemic Update: December 2006". Downloaded from weblink:http://www.unaids.org/en/HIV_data/epi2006/default.asp on 14.05.2007).

Assessment of current use:

Despite the recent progress in treating adults living with HIV, children are not getting the medicines that can prolong their lives. In low- and middle-income countries (most of them in sub-Saharan Africa), about 60,000 to 1,00,000 of the more than 8,00,000 HIV-positive children needing antiretroviral therapy were receiving it in June 2006. Not all the antiretroviral drugs approved for use in adults with HIV exist in an appropriate form, or are licensed and approved, for use in children and those that are available often are unaffordable. Syrup formulations of antiretroviral drugs have been developed, but they tend to be foul tasting, must be taken in large volumes, require refrigeration and have short shelf lives once opened—all of which can make them impractical.

There is an urgent need for affordable, safe, quality ARV formulations appropriate for paediatric use, particularly solid fixed dose combination (FDC) formulations to facilitate programming planning, improve adherence and facilitate scale up of HIV care for children, in line with a public health approach.

Fixed-dose combination drugs, in which two or three different drugs are combined in a single pill to simplify treatment regimens, show excellent clinical, immunological and virological results when used in adults. However, few such drugs are available currently for treating children. (HIV in children: Taking stock: WHO/HIV/2006.04. Downloaded from weblink: **http://www.who.int/entity/hiv/toronto2006/takingstockchildren.pdf,** on 14.05.2007).

Target population:

The FDC would provide the recommended doses of lamivudine, stavudine and nevirapine in paediatric HIV patients weighing between 9-31 Kgs.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

The proposed FDC is in line with NNRTI based triple drug regimen recommended by WHO and National Institute of Health (Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access, Recommendations for a public health approach, World Health Organization 2006; Guidelines for the use of antiretroviral agents in pediatric HIV infection, Oct 2006. National Institute of Health. http://aidsinfo.nih.gov/). The FDC would provide the recommended doses of lamivudine, stavudine and nevirapine in paediatric patients weighing between 9-31 Kgs. This FDC would be suitable for patients who have already received once daily dosing of nevirapine for 14 days. This FDC has to be taken twice daily with or without meals (please refer Table below).

Table. Proposed Dosing Recommendation for Ranbaxy's Fixed Dose Combination of Lamivudine, Stavudine and Nevirapine (Recommended Number of Dispersible Tablets Units Required for Achieving Paediatric Doses)

Patient weight (Kg)	**BSA (m^2)**	**FDC tablets to be given per dose as Low Dose FDC or High Dose FDC**		**Recommended dose of lamivudine, stavudine and nevirapine q12H**			**Actual dose delivered by FDC tablets per dose**		
		Triviro LNS kid	**Triviro LNS kid DS**	**3TC* (mg) 4mg/kg**	**d4T* (mg) 1mg/kg**	**NVP** (mg) 160mg/m^2 to 200mg/m^2**	**Dose Delivered 3TC (mg)**	**Dose Delivered d4T (mg)**	**Dose Delivered NVP (mg)**
09.0	0.424	2	1	36	9	67.88-84.85	40	10	70
10.0	0.459	2	1	40	10	73.51-91.89	40	10	70
11.0	0.496	2.5	-	44	11	79.35-99.19	50	12.5	87.5
12.0	0.534	2.5	-	48	12	85.42-106.78	50	12.5	87.5
13.0	0.569	2.5	-	52	13	90.96-113.70	50	12.5	87.5
14.0	0.606	3	1.5	56	14	96.99-121.24	60	15	105
15.0	0.639	3	1.5	60	15	102.24-127.80	60	15	105
16.0	0.672	3.5	-	64	16	107.46-134.33	70	17.5	122.5
17.0	0.702	3.5	-	68	17	112.40-140.50	70	17.5	122.5
18.0	0.735	3.5	-	72	18	117.58-146.98	70	17.5	122.5
19.0	0.765	4	2	76	19	122.46-153.08	80	20	140
20.0	0.796	4	2	80	20	127.33-159.16	80	20	140
21.0	0.826	4.5	-	84	21	132.18-165.23	90	22.5	157.5
22.0	0.855	4.5	-	88	22	136.73-170.91	90	22.5	157.5
23.0	0.883	4.5	-	92	23	141.26-176.58	90	22.5	157.5
24.0	0.911	5	2.5	96	24	145.77-182.21	100	25	175
25.0	0.937	5	2.5	100	25	149.96-187.45	100	25	175
26.0	0.964	5.5	-	104	26	154.29-192.86	110	27.5	192.5
27.0	0.989	5.5	-	108	27	158.29-197.86	110	27.5	192.5
28.0	1.013	6	3	112	28	162.12-200.00	120	30	210
29.0	1.039	6	3	116	29	166.23-200.00	120	30	210
30.0	1.065	6	3	120	30	170.33-200.00	120	30	210
31.0	1.088	6	3	124	30	174.10-200.00	120	30	210

* Based on body weight (mg/kg) or maximum approved; ** Based on body surface area (mg/m2) or maximum approved.

10. Summary of comparative effectiveness in a variety of clinical settings:

Studies evaluating triple combination of lamivudine, nevirapine and stavudine in paediatric patients are not reported, however a number of studies have evaluated this combination in adults.

Lamivudine, nevirapine and stavudine have been used together in combination with different antiretroviral agents for treatment of HIV infection in paediatric patients in various studies. Also, all three active ingredients of the proposed FDC viz lamivudine, nevirapine and stavudine have been adequately studied in paediatric HIV patients in combination with other antiretrovirals. All three are approved by the US FDA and many other regulatory agencies worldwide for treatment of paediatric HIV patients.

Treatment of therapy-naïve adults with nevirapine plus dual NRTI regimen demonstrated results comparable to triple therapy with the protease inhibitor indinavir (van Leeuwen R et al, 2003), but no similar comparative studies have been performed in children. Results of studies comparing nevirapine-based versus efavirenz-based regimens in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine, with some studies showing more virologic failures with nevirapine and others showing equivalent efficacy of the two drugs (Cozzi-Lepri A et al, 2002; Nunez M et al, 2002; van Leth F et al, 2003). No comparative trials of nevirapine and efavirenz have been conducted in children (Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection Oct, 2006. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the François-Xavier Bagnoud Center, UMDNJ. The Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH). AIDSinfo Web site http://aidsinfo.nih.gov/).

Table. Efficacy and Tolerability of Combination Therapy with Nevirapine + Lamivudine + Stavudine from clinical studies in adults

Reference	**Patient type & Duration of study**	**Efficacy Parameters**				**Tolerability**
		% Pts achieving Viral loads <400 copies/ml	**% Pts achieving Viral loads <50 copies/ml**	**Mean reduction in Plasma HIV RNA levels $\log_{10}$ copies/ml**	**Mean CD4+ cell count increase**	
French M et al. 2002	ARV treatment naïve N = 22 52 weeks	NS	68 %	2.13	113 (cells/μL)	1 patient (5%) ceased assigned treatment due to rash & 3 patients (14%) ceased assigned treatment due to neuropathy. Grade 3 or 4 adverse events were reported in 8(36%) of patients while drug-related grade 3 or 4 adverse events were observed in 5(23%) patients. Other adverse events reported were: raised amylase (5%), raise liver functions tests (10%), headache (5%), chills/fever (5%), other neurological (5%).
Shalit P et al 2001	ARV treatment naïve N = 26 31 months (Median)	NS	92 %	NS	215 cells/ mm^3*	Peripheral neuropathy secondary to stavudine, in 2 cases but no NVP associated side effects. Slight elevation in transaminase levels (after initiating therapy); Increase in SGOT from 26.6 to 28.7 U/l; Increase in SGPT from 25.8 to 38.6 U/l; however the increase in transaminase levels were not clinically relevant.
Yozviak J L et al 2001	ARV treatment experienced N = 73 48 weeks	86.4 % [AT]** 78.1% [ITT]**	84.6%*** 88.9%****	NS	170 (cells/mm^3)	Most common adverse effect reported was rash (13.7%). Other adverse events were: virologic failure (11%). Methadone withdrawal (5.5%) & 2.7% patients discontinued due to this interaction.

[AT]=as-treated analysis; [ITT]= intent to treat analysis; NS= not stated; ARV= antiretroviral.
*Difference between median CD4 cell counts at baseline and last follow up; **at 16 weeks; ***at 24 weeks; ****at 48 weeks.

Raffi F et al, 2001 performed a composite meta-analysis of clinical studies of NNRTI-nevirapine containing, protease inhibitor (PI)-sparing, three-drug highly active antiretroviral therapy (HAART) in HIV- 1-infected, treatment-naive patients. In all of the studies, nevirapine was administered in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). For a study to be included in the analysis, more than 25% of participants must have had baseline viral loads >100,000 copies/mL, and more than 25% of participants must have had viral loads <100,000 copies/mL. After 6 months, 139 of 156 (89%) and 82 of 99 (83%) patients in the low and high baseline viral load groups, respectively, had on-treatment viral loads <200 to 500 copies/mL (depending on assay used). After 12 months, 95 of 124 patients (77%) with lower baseline viral loads and 63 of 76 patients (83%) with high baseline viral loads had on-treatment viral loads below the limit of quantification.

Wiznia A et al 2000 (Pediatric AIDS Clinical Trials Group 377 Study Team) randomised 181 antiretroviral-experienced, protease inhibitor-naive, clinically stable HIV-infected children to receive one of four combination regimens (d4T+NVP+RTV or d4T+3TC+NFV or d4T+NVP+NFV or d4T+3TC+NVP+NFV). Twelve additional children received d4T+3TC+NFV, with NFV given bid, rather than tid as for the main regimens. Overall, 51% (89/176; 95% CI 43-58%) of the children on the randomized portion of the study had an HIV RNA response (400 copies/ml) on at least two of the three HIV RNA determinations taken at Weeks 8, 12, and 16. At Week 24 the proportion of children with an HIV RNA response still on initial therapy was 47% (83/176; 95% CI 40-55%) and ranged from 41 to 61% for the four randomized treatment arms. Rash was frequently seen on the treatment arms containing Nevirapine (a known ADE with nevirapine).

Follow up publication on Pediatric AIDS Clinical Trials Group 377 Study (PACTG 377) by Krogstad P et al 2002, showed that after 48 weeks of therapy, 17 (41%) of 41 subjects receiving d4T-NVP-RTV, 13 (30%) of 44 receiving d4T-NVP-NFV, 21 (42%) of 50 receiving d4T-3TC and NFV (3 times daily), and 22 (52%) of 42 receiving d4T-3TC-NVP-NFV were still receiving their assigned therapy and had HIV-1 RNA suppression to ≤ 400 copies/mL. These regimens were similar in their drug activity, but the 4-drug regimen offered slightly more durable suppression of viremia.

Luzuriaga K et al, 2004 (PACTG 356 Investigators) evaluated the safety, tolerability, and activity of three regimens (ZDV+3TC+NVP or ZDV+3TC+NVP+ABC or D4T+3TC+NVP+NLF) of antiretroviral therapy in a multicenter, open-label, phase 1-2 trial in children infected with HIV-1. Plasma HIV-1 RNA levels fell from a median of 5.3 log copies/ mL (range, 3.3 to 6.4 log copies/ mL) at baseline to less than 1000 copies/ mL at 16 weeks in 32 of 52 infants (62 percent). Plasma HIV-1 RNA levels were below 400 copies/mL at 48 weeks in 26 infants (50 percent) and at 200 weeks in 23 infants (44 percent). Treatment-associated adverse effects were infrequent and no treatment-related adverse effects were reported among children who were receiving the regimen of stavudine + lamivudine + nevirapine + nelfinavir.

11. Summary of comparative evidence on safety:

Estimate of total patient exposure to date:

To date following quantity of Triviro LNS Kid (LNS -20/35/5) and Triviro LNS Kid DS (LNS -40/70/10) have been sold in the countries stated.

Country	Triviro LNS Kid (LNS -20/35/5)	Triviro LNS Kid DS (LNS -40/70/10)
India	-	112,401 packs of 60s
Papua New Guinea	-	1,688 packs of 60s
Mozambique	42,975 packs of 60s	-
Jamaica	1,200 packs of 60s	-

Description of adverse effects/reactions:
With the use of the fixed dose combination, adverse events associated with lamivudine, nevirapine and stavudine may be expected. The adverse events reported in patients, who were on concomitant therapy with nevirapine, lamivudine and stavudine, in clinical studies are summarized below.

Table. Adverse events reported in patients, who were on comcomitant therapy with nevirapine, lamivudine and stavudine (French M et al. 2002, Shalit P et al. 2001,Yozviak J L et al. 2001, Laurent C et al, 2004).

Reference	Patient Population	No. of pts	Duration	Tolerability
French M et al. 2002	ARV Treatment-naïve	22	52 weeks	1 patient (5%) ceased assigned treatment due to rash & 3 patients (14%) ceased assigned treatment due to neuropathy. Grade 3 or 4 adverse events were reported in 8(36%) of patients while drug-related grade 3 or 4 adverse events were observed in 5(23%) patients. Other adverse events reported were: raised amylase (5%), raise liver functions tests (10%), headache (5%), chills/fever (5%), other neurological (5%).
Shalit P et al. 2001	ARV Treatment-naïve	26	31 months (Median)	Peripheral neuropathy secondary to stavudine, in 2 cases but no NVP associated side effects. Slight elevation in transaminase levels (after initiating therapy); Increase in SGOT from 26.6 to 28.7 U/l; Increase in SGPT from 25.8 to 38.6 U/l; however the increase in transaminase levels was not clinically relevant.
Yozviak J L et al. 2001	ARV Treatment experienced	73	48 weeks	Most common adverse effect reported was rash (13.7%). Other adverse events were: virologic failure (11%). Methadone withdrawal (5.5%) & 2.7% patients discontinued due to this interaction.

Reference	Patient Population	No. of pts	Duration	Tolerability
Laurent C et al, 2004	Patients with confirmed HIV-1 group M infection, & who had not taken antiretroviral before	60	24 weeks	5 severe (grade 3) adverse effects were attributed to study treatment (incidence 17.8 per 100 person-years,). 1 patient developed generalized urticaria 13 days after starting treatment and had raised ALT (274 U/L); both disorders resolved when nevirapine was replaced with indinavir. 2 other individuals had increased ALT (311 U/L and 158 U/L) after 2 and 6 weeks of treatment, respectively; concentrations returned to normal spontaneously in one and fell to 88 U/L in the second. Finally, 1 patient had a transient amylase rise at 24 weeks (521 U/L) with no clinical signs of pancreatitis. The treatment was not discontinued in these patients. No cases of grade 3 peripheral neuropathy were recorded, only three cases of grade 1 and one of grade 2. No grade 4 adverse events occurred. The mean self-reported adherence rate was 99%. Only nine patients reported incidents relating to adherence: five did not take the study treatment at all during the last 7 days either because they did not attend (n=3) or postponed (n=1) the relevant study visit or because of a psychiatric disorder (n=1); three patients forgot one dose; and one missed four doses owing to dizziness.

Adverse drug reactions

Lamivudine

Adults: Selected clinical adverse events with a ≥5% frequency during therapy with lamivudine 150 mg twice daily plus zidovudine 200 mg 3 times daily compared with zidovudine have been listed in table below.

Table. Selected Clinical Adverse Events (≥5% frequency) in Four Controlled Clinical Trials.

Adverse Event	**Lamivudine 150 mg twice daily plus zidovudine**	**Zidovudine***
Body as a whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous system		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.

Pancreatitis was observed in patients (0.3%) who received lamivudine in the controlled clinical trials.

Selected laboratory abnormalities observed during therapy have been summarized in table below.

Table. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies And a Clinical Endpoint Study.

Test (Threshold Level)	**24- Week Surrogate Endpoint Studies***		**Clinical Endpoint Study***	
	Lamivudine + Zidovudine	**Zidovudine****	**Lamivudine +Current Therapy**	**Placebo + Current Therapy*****
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm^3)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 x ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 x ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 x ULN)	4.2%	1.5%	2.2%	1.1%

*The median duration on study was 12 months.
.** Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
.***Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.
ULN = Upper limit of normal.
ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy, reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving lamivudine 300 mg once daily or lamivudine 150 mg twice daily (in 3-drug combination regimens) were similar.

Pediatric patients: Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) paediatric patients have been listed in table below.

Table. Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Paediatric Patients.

Adverse Event	Lamivudine plus Zidovudine	Didanosine
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhoea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) paediatric patients have been listed in table below.

Table. Frequencies of Selected Laboratory Abnormalities in Pediatric Patients.

Test (Threshold level)	Lamivudine plus Zidovudine	Didanosine
Absolute neutropenia count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN=Upper limit of normal

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced paediatric patients receiving lamivudine alone or in combination with other antiretroviral agents. In an open-label dose-escalation study, 14 patients (14%) developed pancreatitis while receiving monotherapy with lamivudine. Three of these patients died of complications of pancreatitis. In a second open-label study, 12 patients (18%) developed pancreatitis. In one of the clinical trial, pancreatitis was not observed in 236 patients randomized to lamivudine plus zidovudine. Pancreatitis was observed in 1 patient in this study who received open-label lamivudine in combination with zidovudine and ritonavir following discontinuation of didanosine monotherapy.
Paresthesias and peripheral neuropathies were reported.

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at week 38 or 36 of gestation. Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, and syphilis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from

traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups further limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.
Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and post treatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported.

Observed during clinical practice
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. Because they are 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, frequency of reporting, or potential causal connection to lamivudine.
Body as a Whole: Redistribution/accumulation of body fat.
Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B.
Hypersensitivity: Anaphylaxis, urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, rash, pruritus.
(US Prescribing Information *EPIVIR,* Oct 2006).

Nevirapine

The most serious adverse reactions associated with nevirapine are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Clinical hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction.

Adults

The most common clinical toxicity of nevirapine is rash which can be severe or life-threatening. Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2 rashes were reported in 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine associated rash.

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm3 in women and >400 cells/mm^3 in men) place patients at increased risk of these events.

Asymptomatic transaminase elevations (AST or ALT > 5X ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table below.

Table. Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials.

	Nevirapine[1] n=1121	**Placebo[1] n=1128**	**Nevirapine[2] n=253**	**Placebo[2] n=203**
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

[1]Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.; [2]Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm^3.

Laboratory Abnormalities: Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls. Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (table below).

Table. Percentage of Adults Patients with Laboratory Abnormalities.

Laboratory Abnormality	Nevirapine[1] n=1121	Placebo[1] n=1128	Nevirapine[2] n=253	Placebo[2] n=203
Blood Chemistry				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
Hematology				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm^3	1.3	1.0	0.4	1.5
Neutrophils <750/mm^3	13.3	13.5	3.6	1.0

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.; [2] Background therapy included ZDV and ZDV+ ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm^3.

Because clinical hepatitis has been reported in nevirapine-treated patients, intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment. Monitoring should continue at frequent intervals thereafter, depending on the patient's clinical status.

Observed during clinical practice

In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine in clinical practice:

Body as a Whole: Fever, somnolence, drug withdrawal, redistribution/accumulation of body fat.

Gastrointestinal: Vomiting

Liver and Biliary: Jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure

Hematology: Anemia, eosinophilia, neutropenia

Musculoskeletal: Arthralgia

Neurologic: Paraesthesia

Skin and Appendages: Allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

Paediatric Patients

Safety was assessed in trial in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients). The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children. Serious adverse events were assessed in, a double-blind, placebo-controlled trial of nevirapine in which pediatric patients received combination treatment with nevirapine. In this trial two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases

of allergic reaction, including one case of anaphylaxis, were also reported. . In post-marketing surveillance anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.
(Prescribing Information of *VIRAMUNE*, Boehringer Ingelheim Pharmaceuticals Inc., USA, April 2007).

Stavudine
Adults: Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.
Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.
Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with neurotoxic drug therapy, including didanosine, in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.
Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose. If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.
When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea.
Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study have been listed in table below.

Table. Selected Clinical Adverse Events in Adult Patients Receiving Stavudine in a Controlled Monotherapy Study*

Adverse Events	**Percentage (%)**	
	Stavudine (40mg twice daily)	Zidovudine (200mg 3 times daily)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

*Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy =53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral naive adult patients receiving stavudine from two controlled combination studies have been listed in table below.

Table. Selected Clinical Adverse Events in Antiretroviral Naive Adult Patients Receiving Stavudine From Two Controlled Combination Studies.

Adverse Events	Percent (%)			
	Study 1		Study 2*	
	Stavudine+ Lamivudine+ Indinavir**	Zidovudine+ Lamivudine + Indinavir	Stavudine+ Didanosine+ Indinavir**	Zidovudine + Lamivudine+ Indinavir
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

* Study 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either Stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

**Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study have been listed in table below.

Table. Selected Adult Laboratory Abnormalities in a Controlled Monotherapy Study [a, b]

Parameter	Percent (%)	
	Stavudine (40 mg twice daily)	Zidovudine (200 mg 3 times daily)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

[a] Data presented for patients for whom laboratory evaluations were performed.

[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

ULN = upper limit of normal.

Selected laboratory abnormalities reported in two-controlled combination studies have been listed in table below.

Table: Selected Laboratory Abnormalities in Two Controlled Combination Studies (Grades 3-4).

Parameter	Percent (%)			
	Study 1		Study 2	
	Stavudine + Lamivudine + Indinavir (n=100)	Stavudine + Lamivudine + Indinavir (n=102)	Zidovudine + didanosine + Indinavir (n=102)	Zidovudine + lamivudine + Indinavir (n=103)
Bilirubin (>2.6 x ULN)	7	6	16	8
AST (SGOT) (>5 x ULN)	5	2	7	7
ALT (SGPT) (>5 x ULN)	6	2	8	5
GGT (>5 x ULN)	2	2	5	2
Lipase (>2 x ULN)	6	3	5	5
Amylase (>2 x ULN)	4	<1	8	2
ULN = upper limit of normal.				

Table. Selected Laboratory Abnormalities in Two Controlled Combination Studies.

Parameter	Percent (%)			
	Study 1		Study 2	
	Stavudine+ Lamivudine+ Indinavir	Zidovudine+ Lamivudine+ Indinavir	Stavudine +Didanosine+ Indinavir	Zidovudine+ Lamivudine +Indinavir
Total bilirubin	65	60	68	55
SGOT (AST)	42	20	53	20
SGPT (ALT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

Paediatric Patients*:* Adverse reactions and serious laboratory abnormalities in paediatric patients from birth through adolescence were similar in type and frequency to those seen in adult patients.

Observed during clinical practice

The following events have been identified during post-approval use of stavudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

Body as a Whole: abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat.

Digestive Disorders: anorexia.

Exocrine Gland Disorders: pancreatitis [including fatal cases].

Hematologic Disorders: anemia, leukopenia, and thrombocytopenia.

Liver: lactic acidosis and hepatic steatosis, hepatitis and liver failure.

Musculoskeletal: myalgia.

Nervous System: insomnia, severe motor weakness (most often reported in the setting of lactic acidosis).

(Prescribing Information of *ZERIT*, Bristol-Myers Squibb company, USA, Aug 2006).

Identification of variation in safety due to health systems and patient factors

In paediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine should be used with caution. Treatment with lamivudine should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

Patients With Impaired Renal Function: The effect of renal impairment on lamivudine pharmacokinetics in paediatric patients is not known. Reduction of the dosage of lamivudine is recommended for patients with impaired renal function.

The safety and pharmacokinetic properties of lamivudine in combination with antiretroviral agents other than zidovudine have not been established in paediatric patients.

Severe acute exacerbations of hepatitis B infection have been reported in HBV/HIV co-infected patients upon discontinuation of lamivudine-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of lamivudine in patients with HIV/HBV co-infection. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Nevirapine should not be used in post-pubertal adolescent girls with CD4 count > 250 cells/mm^3 due to the increased risk of symptomatic hepatotoxicity, unless the benefit clearly outweighs the risk.

Summary of comparative safety against comparators

A bioequivalence study had been conducted by the Applicant comparing lamivudine 40 mg, nevirapine 70 mg and stavudine 10 mg fixed-dose combination tablet for oral suspension (Ranbaxy Laboratories Limited) with 4 mL of Epivir oral solution (containing lamivudine 10 mg/mL, GlaxoSmithKline), 7 mL of Viramune oral suspension (containing nevirapine 50 mg/5mL, Boehringer Ingelheim Pharmaceuticals Inc.) and 10 mL of Zerit oral solution (containing stavudine 1 mg/mL, Bristol-Myers Squibb).

Safety Results

The adverse events reported during the conduct of this study are tabulated below.

Table. Adverse Events Reported During BE Study No. 105_LAMNS_06

Subject No	Period No.	Adverse Event	Onset time from Last Dosing (hours)	Duration of adverse event (hours)	SEVERITY/ SERIOUSNESS	Interventions/ Medication prescribed to treat adverse event	Outcome	Study Medication	Relationship
07	Period I	Dizziness	3.5	1.333	Moderate/Non Serious	1) Glucon D - 04 table spoonful orally on 16 May 2006 2) Dextrose injection 25% w/v. 100 ml IV on 16 May 2006 3) Ringers lactate. 500 ml I/V on 16 May 2006	Resolved	Reference	Probable
07	Period I	Headache	3.5	1.333	Moderate/Non Serious		Resolved	Reference	Probable
28	Period I	Abrasion over the right arm	52.4	76.5	Mild/Non Serious	1) Band-aid (Benzalkonium hydrochloride 0.5% w/w) on 19 May 2006 (Total dose = 01) 2) Betadine lotion (Povidone iodine 5% w/v). Single application from 19 May 2006 to 21 May 2006 (Total doses = 03) 3) Injection tetanus toxoid. IM Stat on 19 May 2006 (Total dose = 01)	Resolved	Test	None
16	Period II Predose	Folliculitis	550.4	96.5	Mild/Non Serious	1) Tablet Brufen (Ibuprofen 400 mg). 2 oral doses on 08 June 2006 2) Capsule Phexin-250 mg (Cephalexin 250 mg). Stat on 08 June 2006. Then QID from 08 June 2006 to 13 June 2006. (Total doses= 20)	Resolved	Test	Possible
08	Period II	Dizziness	0.967	1.5	Mild/Non Serious	None	Resolved	Reference	Possible

Dates of Dosing
Period I: **May 16, 2006**
Period II: June 08, 2006

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

Range of costs of the proposed medicine
Triviro LNS kid = per unit cost = USD 0.045
Triviro LNS kid DS = per unit cost = USD 0.095

Comparative cost-effectiveness presented as range of cost per year of treatment for a child weighing 10 Kg.

Formulation	***Cost per year of treatment* (USD)***
Triviro LNS kid	**64.8**
Epivir® **+** **Zerit ®** **+** **Viramune ®**	**82** **51** **=** **534** **401**
Cost Benefit/per year of treatment	**469.2**
***** Source: Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries. 9th Edition, July 2006 downloaded from website www.accessmed-msf.org on 14/05/2007.	

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Regulatory Status

Country	Product Name	Generic Name	Registration Status
India	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Approved
Nigeria	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Approved
Cambodia	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Cameroon	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Congo	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Gabon	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Ivory Coast	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Kenya	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration

Country	Product Name	Generic Name	Registration Status
Malawi	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Malaysia	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Myanmar	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Tanzania	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Uganda	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Zambia	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Zimbabwe	Triviro LNS Kid DS Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
India	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Approved
Nigeria	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Approved
Cambodia	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Cameroon	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Congo	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Gabon	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Ivory Coast	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Kenya	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Malawi	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Malaysia	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Myanmar	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral	Under Registration

Country	Product Name	Generic Name	Registration Status
		Suspension	
Tanzania	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Uganda	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Zambia	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration
Zimbabwe	Triviro LNS Kid Tablets	Lamivudine, Nevirapine and Stavudine Tablets for oral Suspension	Under Registration

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

All the three active ingredients are official in USP.

15. Proposed (new/adapted) text for the WHO Model Formulary Summary statement of the proposal for inclusion:
Draft WHO Model Formulary for Lamivudine plus Stavudine and Nevirapine.

The following is based on Product Information for Triomune tablets and the WHO model formulary for each individual component.
Source: (http://mednet3.who.int/EMLib/modelFormulary/modelFormulary.asp).
Name:
Lamivudine,
PLUS
Stavudine
PLUS
Nevirapine used in the treatment of HIV infection.
Composition:

Tablets for oral suspension, containing

Triviro LNS kid DS: Lamivudine 40 mg, Stavudine 10 mg, Nevirapine70 mg

Triviro LNS kid: Lamivudine 20 mg, Stavudine 5 mg, Nevirapine 35 mg

Use:
For the treatment for HIV-1 infection in children. . Lamivudine and stavudine are Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and nevirapine is a Non-Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NNRTI).
Dosage and administration:
Lamivudine plus stavudine plus nevirapine:
Treatment with the fixed combination should not be started on Day 1. For the first two weeks, your doctor will tell you to start therapy by taking nevirapine, lamivudine and stavudine separately for the first two weeks. If during this period you experience no rash or other side effects, your doctor will instruct you to start therapy with the fixed dose combination.
Triviro Kid/Kid DS (the fixed dose combination) should be taken by mouth twice daily, with or without food.

Table. Proposed Dosing Recommendation for Ranbaxy's Fixed Dose Combination of Lamivudine, Stavudine and Nevirapine (Recommended Number of Dispersible Tablets Units Required for Achieving Paediatric Doses)

Patient weight (Kg)	FDC tablets to be given per dose as Low Dose FDC or High Dose FDC	
	Triviro LNS kid	Triviro LNS kid DS
09.0	2	1
10.0	2	1
11.0	2.5	-
12.0	2.5	-
13.0	2.5	-
14.0	3	1.5
15.0	3	1.5
16.0	3.5	-
17.0	3.5	-

Patient weight (Kg)	FDC tablets to be given per dose as Low Dose FDC or High Dose FDC	
	Triviro LNS kid	Triviro LNS kid DS
18.0	3.5	-
19.0	4	2
20.0	4	2
21.0	4.5	-
22.0	4.5	-
23.0	4.5	-
24.0	5	2.5
25.0	5	2.5
26.0	5.5	-
27.0	5.5	-
28.0	6	3
29.0	6	3
30.0	6	3
31.0	6	3

Contraindications and precautions for use:
Lamivudine plus stavudine plus nevirapine:
HYPERSENSITIVITY REACTION
Since Triviro Kid/Kid DS contains nevirapine, some patients taking Triviro Kid/Kid DS may develop a hypersensitivity reaction (a serious allergic reaction). Patients may develop severe liver disease or skin reactions that may be life-threatening. The risk of these reactions is greatest during the first 6 weeks of treatment. Your doctor should check you clinically and do liver function tests (blood tests) often in the first 6 weeks of therapy. These reactions can also occur later and checks for liver problems should continue regularly during your therapy. Patients with significant altered liver function tests and patients with clinical hepatitis B or C may have an increased chance of liver toxicity while taking nevirapine and should be carefully monitored. Patients with higher CD4 counts, particularly HIV+ women with CD4 cell counts $\geq 250/mm^3$ and HIV+ men with CD4 counts $\geq 400/mm^3$, seem to have a greater chance of developing a rash with associated liver damage while taking nevirapine, even in the absence of concomitant hepatic disease.
In rare cases liver problems have led to liver failure, which can lead to liver transplants or death. Therefore, if you develop any of the following symptoms of liver problems, inform your doctor right away:
• General ill feeling or “flu-like” symptoms
• Tiredness
• Nausea (feeling sick to your stomach)
• Lack of appetite
• Yellowing skin or whites of your eyes
• Dark urine
• Pale stools (bowel movements)
• Pain, ache, or sensitivity to touch on your right side below your ribs

Nevirapine can cause serious skin rash. Skin rash is the most common side effect of nevirapine. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, rash can be serious and result in death. Therefore, if you develop a rash with any of the following symptoms, stop using Triviro Kid/Kid DS and inform your doctor right away:
• General ill feeling or “flu-like” symptoms
• Fever
• Muscle or joint aches

• Tiredness
• Conjunctivitis (red or inflamed eyelids)
• Blisters
• Mouth sores
• Swelling of your face

If your doctor tells you to stop treatment with Triviro Kid/Kid DS because you have these types of serious reactions, never take Triviro Kid/Kid DS again.

Changes in body fat have been seen in some patients taking long term antiretroviral therapy, this is called lipodystrophy syndrome. These changes may include loss of fat from the legs, arms and face, increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk and increase in blood triglycerides and cholesterol levels may also happen. The cause and long-term health effects of these conditions are not well known at this time.
The class of medicines to which both stavudine and lamivudine belong (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect occurs more frequently in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Triviro Kid/Kid DS, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.
Stavudine can cause a neurological condition known as peripheral neuropathy. If this happens, the symptoms are numbness, tingling, or pain in the hands or feet and you should inform your doctor immediately. Neuropathy occurs with greatest frequency in patients with advanced HIV disease or in patients who have suffered from peripheral neuropathy in the past. If neuropathy develops, the dose of stavudine may need to be reduced, and therapy with Triviro Kid/Kid DS may no longer be appropriate. Your doctor will advise you regarding this.
If you have hepatitis B infection, you should not stop your treatment without instructions from your doctor, as you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.
Pregnancy
Inform your doctor if you are pregnant or planning to become pregnant. Triviro Kid/Kid DS should be taken during pregnancy only after consultation with your doctor.
Breast feeding
Inform your doctor if you are breastfeeding. Some health experts recommend that HIV-infected women should not breastfeed their infants in order to avoid transmission of HIV.
Driving and using machines
No studies on the effects of Triviro Kid/Kid DS on the ability to drive and use machines have been performed. However, you should take into account the state of your health and the possible side effects of Triviro Kid/Kid DS before considering driving or using machines.

Taking Triviro Kid/Kid DS with other medicines
Please inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed. Triviro Kid/Kid DS should not be taken with zidovudine, zalcitabine, ketoconazole, rifampin and clarithromycin. Triviro Kid/Kid DS may interact with certain other medicines, which may make side effects worse. It is important that you tell your doctor if you are taking any of the following medicines (ask your doctor if you are not sure):
- trimethoprim/sulfamethoxazole
- efavirenz
- rifabutin
- fluconazole
- indinavir

- lopinavir/ritonavir
- warfarin
- ganciclovir
- foscarnet

Furthermore, nevirapine can reduce the efficacy of oral contraceptive pills. Hence, oral contraceptives should not be used as the sole method of contraception. An alternative or additional method of contraception is recommended.
If you are taking methadone, your doctor may need to adjust your methadone dose.
It is important that your doctor knows about all the medicines you are taking. Tell your doctor about all the medicines you are taking, including vitamin supplements, herbal remedies or homeopathic remedies including those you have bought yourself, as well as drugs not listed above.
Adverse effects:
Lamivudine plus stavudine plus nevirapine:
Serious side effects that may occur with the use of the fixed dose combination are:
• Lactic acidosis (severe increase of lactic acid in the blood), severe liver enlargement, including inflammation (pain and swelling) of liver and liver failure, which can cause death.
Symptoms of lactic acidosis may include:
• Nausea, vomiting, or unusual or unexpected stomach discomfort
• Feeling very weak and tired
• Shortness of breath
• Weakness in arms and legs

Inform your doctor immediately if you experience any of the following symptoms.
• Peripheral neuropathy, a nerve disorder of the hand and feet. This nerve disorder is rare, but may be serious. If you have numbness, tingling, burning, or pain in the feet and/or hands, inform your doctor immediately.
• Pancreatitis is a dangerous inflammation of the pancreas. It may cause death. Tell your doctor right away if you develop stomach pain, nausea or vomiting. These can be signs of pancreatitis.
• Loss of fat from the legs, arms and face.
• Severe, life-threatening, and in some cases fatal liver disease (hepatitis, liver failure) and skin reactions have been reported. In a small number of patients, rash has been severe and has resulted in death.

Combination antiretroviral therapy may also cause raised sugar in the blood, hyperlipidaemia (increased fats in the blood) and resistance to insulin.

Individual Components:
Lamivudine:
nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red-cell aplasia; lactic acidosis; raised liver enzymes and serum amylase reported.
Stavudine:
peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; abnormal dreams, cognitive dysfunction, drowsiness, depression, anxiety; gynaecomastia; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes and serum amylase; neutropenia, thrombocytopenia.
Nevirapine:
The most clinically important adverse events associated with nevirapine therapy are rash and increases in liver function tests. Cases of hypersensitivity reactions have been observed.

The major clinical toxicity of nevirapine is rash, with nevirapine-attributable rash occurring in 16% of patients in combination regimens in Phase II/III controlled studies. Thirty-five percent of patients treated with nevirapine experienced rash compared with 19% of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life-threatening rash occurred in 6.6% of nevirapine-treated patients compared with 1.3% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions; with or without pruritus, located on the trunk, face and extremities. The majority of severe rashes occurred within the first 28 days of treatment. 25% of the patients with severe rashes required hospitalization, and one patient required surgical intervention. Overall, 7% of patients discontinued nevirapine due to rash.

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