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 zidovudine are recommended preferred first-line drugs for 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 zidovudine (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/). The doses of the individual components of the proposed FDC are lamivudine 30 mg, zidovudine 60 mg and nevirapine 60 mg. The FDC would provide the recommended doses of lamivudine, zidovudine and nevirapine in paediatric patients weighing between 9-24.9 Kgs.

The safety and efficacy of Lamivudine, zidovudine and nevirapine in the treatment of HIV patients has been established in various clinical trials. Lamivudine, nevirapine and zidovudine 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 zidovudine.

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

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

World Health Organization.

4. International Nonproprietary 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
- Zidovudine
- Nevirapine

5. **Dosage form or strength proposed for inclusion**

The Ranbaxy's formulation will be available as tablets for oral suspension. The composition of proposed FDC is:

FDC Components	Dose
Lamivudine	30 mg
Zidovudine	60 mg
Nevirapine	60 mg

6. **International availability - sources, if possible manufacturers**

Product is currently under development by Ranbaxy Laboratories Limited, India.

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. About 60,000 to 1, 00,000 of the more than 8,00,000 HIV-positive children, in low- and middle-income countries, needing antiretroviral therapy (most of them in sub-Saharan Africa) 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. 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, zidovudine and nevirapine in paediatric HIV patients weighing between 9-24.9 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, zidovudine and nevirapine in paediatric patients weighing between 9-24.9 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, Zidovudine and Nevirapine (Recommended Number of Dispersible Tablets Units Required for Achieving Pediatric Doses)

Patient weight (Kg)	BSA (m^2)	FDC tablets to be given per dose	Recommended dose of lamivudine (3TC), Zidovudine(AZT) and nevirapine (NVP) q12H					Actual dose delivered by FDC tablets per dose		
			3TC (mg) [4 mg/kg]	AZT[@] (mg) [180 mg/m^2]	AZT[#] (mg) [240 mg/m^2]	NVP (mg)[*] [160 mg/m^2]	NVP (mg)[+] [200 mg/m^2]	3TC (mg)	AZT (mg)	NVP (mg)
9.0 - 9.9	0.43 - 0.45	1.5	36.0 - 39.6	76.5-81	102-108	68.0 - 72.0	85.0 - 90.0	45.0	90.0	90.0
10.0 - 10.9	0.45 - 0.49	1.5	40.0 - 43.6	81-87.8	108-117.1	72.0 - 78.1	90.0 - 97.6	45.0	90.0	90.0
11.0 - 11.9	0.49 - 0.53	1.5	44.0 - 47.6	87.8-94.5	117.1-126	78.1 - 84.0	97.6 - 105.0	45.0	90.0	90.0
12.0 - 13.9	0.53 - 0.58	2	48.0 - 55.6	94.5-103.5	126-138	84.0 - 92.0	105.0 - 115.0	60.0	120.0	120.0
14.0 - 16.9	0.58 - 0.70	2	56.0 - 67.6	103.5-126	138-168	92.0 - 112.0	115.0 - 140.0	60.0	120.0	120.0
17.0 - 19.9	0.70 - 0.80	2.5	68.0 - 79.6	126-144	168-192	112.0 - 128.0	140.0 - 160.0	75.0	150.0	150.0
20.0 - 24.9	0.80 - 0.95	3	80.0 - 99.6	144-168.7	192-200	128.0 - 152.0	160.0 - 190.0	90.0	180.0	180.0

[@] Zidovudine dosage calculation at 180mg/m^2 body surface area
[#] Zidovudine dosage calculation at 240mg/m^2 body surface area
[*] Nevirapine dosage calculation at 160mg/m^2 body surface area
[+] Nevirapine dosage calculation at 200mg/m^2 body surface area

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

Lamivudine, zidovudine and nevirapine have been used together in combination with different antiretroviral agents for treatment of HIV infection in pediatric patients in various studies, which suggest that this combination has a reasonable tolerability profile.

Also, all three active ingredients of the proposed FDC viz lamivudine, zidovudine and nevirapine have been adequately studied in pediatric HIV patients in combination with other antiretrovirals. All three are approved by the US FDA and many other regulatory agencies worldwide for treatment of pediatric HIV patients.

Clinical Studies with Lamivudine, Nevirapine and Zidovudine Combination:

Pediatric

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.

Adult

The effectiveness of triple combination therapy in antiretroviral-naive patients were reviewed (Bartlett JA et al, 2001). Data from 23 clinical trials involving triple combination therapy with dual nucleoside reverse transcriptase inhibitors and: a protease inhibitor (PI triple); a non-nucleoside reverse transcriptase inhibitor (NNRTI triple); or a third NRTI (triple NUC). Median log10 baseline plasma HIV RNA and CD4 cell count over all trials averaged 4.69 (49,329 copies/ml) and 375 x 106 cells/l, respectively. The overall estimated percentage of patients with plasma HIV RNA ≤ 400 copies/ml at 24 weeks was 64% [95% confidence interval (CI), 60 to 67%]. The percentages of patients with plasma HIV RNA ≤ 50 copies/ml at 48 weeks by drug class were: PI triple, 46% (95% CI, 41 to 52%); NNRTI triple, 51% (95% CI, 43 to 59%); triple NUC, 45% (95% CI, 36 to 54%). The CD4 cell count increased over all trials at 24 and 48 weeks averaged +123 x 106 cells/l (95% CI, 111 x 106 to 135 x 106 cells/l) and +160 x 106 cells/l (95% CI, 146 x 106 to 175 x 106 cells/l), respectively and did not differ between drug classes. In multivariable regression analysis, neither baseline plasma HIV RNA level and CD4 cell count nor treatment regimen predicted plasma HIV RNA ≤ 50 copies/ml at week 48. However, pill count was significantly negatively associated with plasma HIV RNA ≤ 50 copies/ml at week 48 (P = 0.0085). The results suggested that three drug regimens containing two NRTI with a NNRTI, or a third NRTI may provide comparable activity.

Casado A et al, (2004) conducted a study to assess differences in health-related quality of life (HRQoL) in HIV-infected naive patients treated with two HAART regimens at 12 months. In this study the MOS-HIV questionnaire was used to measure HRQoL in a subgroup of 127 patients included in the COMBINE STUDY, which was an open-label, randomized, multicenter study comparing zidovudine (ZDV) and lamivudine (3TC) plus nelfinavir (NFV) or nevirapine (NVP) regimens in HIV-infected naive patients. 63 patients were included in the ZDV/3TC/NFV arm and 64 in the ZDV/3TC/NVP arm. No statistically significant differences were observed at baseline in demographic and clinical variables and HRQoL scores between treatment groups, except that the proportion of homosexual men was higher in the ZDV/3TC/NVP arm. There were no statistically

significant differences in HRQoL scores between arms at 12 months and over time; only ZDV/3TC/NVP patients showed statistically significant improvement in Physical Health Summary score ($p < .01$) and a trend toward a better profile in Mental Health Summary score ($p = .07$). Overall, patients who were treated with ZDV/3TC/NVP showed greater changes in physical dimensions and with ZDV/3TC/NFV showed greater changes in mental health. The authors concluded that differences in HRQoL between study groups at 1 year follow-up were not detected. Nevertheless, a trend toward improvement was observed in summary health scores in ZDV/3TC/NVP-treated patients.

French M et al (2002) evaluated the efficacy and safety of three triple combination antiretroviral therapies in seventy treatment-naive HIV-infected adults with CD4+ T-cell counts >50/μL. Patients were randomized to receive either zidovudine + lamivudine + nevirapine (AZT + 3TC + NVP), stavudine + didanosine + nevirapine (d4T+ddI+NVP), or stavudine + lamivudine + nevirapine (d4T+3TC+NVP) for 52 weeks. Patient assessments were conducted monthly and included measurement of plasma HIV RNA levels and CD4+ T-cell counts and evaluations for drug toxicity. The mean time-weighted reductions in plasma HIV RNA in the AZT+3TC+NVP, d4T+3TC+NVP, and d4T+ddI+NVP groups were 1.29, 2.13, and 1.78 log10 copies/mL, respectively ($p= 0.389$). The proportions of patients with HIV RNA <50 copies/mL in the AZT+3TC+NVP, d4T+3TC+NVP, and d4T+ddI+NVP groups were 73%, 68%, and 80%, respectively ($p= 0.71$). The mean time-weighted increases in CD4+ T-cell counts in the AZT+3TC+NVP, d4T+3TC+NVP, and d4T+ddI+NVP groups were 139, 113, and 174 cells/μL, respectively ($p= 0.30$). Three patients discontinued assigned treatment due to rash (one from each treatment arm), and 5 of the 45 patients on d4T (3 from the d4T+3TC+NVP arm and 2 from the d4T+ddI+NVP arm) discontinued assigned treatment due to neuropathy. All three-drug combinations were equally effective at suppressing viral load and increasing CD4+ T-cell counts. No significant differences were detected between the treatment groups in virological or immunological response or cessation of study drugs due to adverse events. NVP was safe and efficacious in this setting, and efficacy was not influenced by nucleoside reverse transcriptase inhibitor backbone.

Plana M et al, (2004) conducted a study to evaluate the immunological response in HIV-1-infected, antiretroviral-naive patients receiving highly active antiretroviral therapy regimen of two nucleosides plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Of 142 patients included in a randomized, open, multicentre trial comparing zidovudine/lamivudine plus nelfinavir (NFV) or nevirapine (NVP), 36 patients (16 NFV, 20 NVP) were enrolled in an immunological substudy. Mean baseline CD4 T-cell counts was 360/ mm3 (range: 11-679) and mean baseline plasma viral load >50000 copies/ml (range: 2240-1468210). Viral load (VL), T-cell subsets and T-cell functions were analysed at baseline and after 1 year of treatment. After 12 months of follow-up, plasma viral load was reduced similarly in both groups, with 78% (NFV) and 83% (NVP) of patients achieving a VL <200 copies/ml. A significant increase in CD4 T cells was observed in both groups (mean: +182 cells, $P=0.001$). Both regimens were similarly effective in reducing activated T cells (CD38 and DR). A significant increase of both CD4 and CD8 CD28 T cells occurred in both arms of treatment. Patients of both regimens showed a significant decrease of activated memory (CD45RA-CD45RO+) CD8 T cells and a clear increase of naive (CD45RA+CD45RO-) CD8 T cells. Peripheral blood mononuclear cell proliferative responses to polyclonal stimuli (CD3 and CD3 +CD28) as well as to ubiquitous cytomegalovirus antigen increased significantly in both groups after 12 months of follow-up. Nevertheless, neither at baseline nor after 1 year of treatment, these patients showed any significant T-cell responsiveness to HIV-1 recombinant proteins gp160 or p24. The authors concluded that immune restoration achieved after 1 year of therapy with either NFV or NVP was similar.

Podzamczer D et al (2002) in a randomized, open-label, multicentre trial evaluated the efficacy and safety of nevirapine or nelfinavir associated with zidovudine/lamivudine in 142 HIV-infected treatment naive patients without AIDS. Patients received zidovudine 300 mg/lamivudine 150 mg, twice-daily plus either nelfinavir 1250 mg or nevirapine 200 mg twice-daily and were followed for 12 months. The primary endpoint was the proportion of patients with plasma HIV-1 RNA (pVL) of less than 200 copies/ml by PCR at 12 months. pVL of less than 20 copies/ml (PCR), changes in CD4 counts, clinical progression and adverse events were also evaluated. At 12 months in the intention-to-treat analysis the proportion of patients with plasma HIV-1 RNA (pVL) below 200 copies/ml was 60% in the zidovudine/lamivudine/nelfinavir arm and 75% in the zidovudine/lamivudine/nevirapine arm (p= 0.06), and the proportion below 20 copies/ml was 50% and 65%, respectively (p= 0.06). No differences were found when comparing the subgroup of patients with baseline pVL of more than 100,000 copies/ml. A gain of +173 and +162 CD4 + cells/mm3, respectively, was observed. Zidovudine/lamivudine/nelfinavir was discontinued in 21% of patients, and zidovudine/lamivudine/nevirapine in 25%, due to toxicity (p > 0.2). The results suggested that zidovudine/lamivudine/nevirapine is at least as effective as zidovudine/lamivudine/nelfinavir as first-line therapy for HIV disease.

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).

A summary of clinical studies evaluating the efficacy and safety of the three drug combinations-nevirapine, lamivudine and zidovudine is given in following table:

Table. Summary of clinical studies evaluating the efficacy and safety of the three drug combinations- nevirapine, lamivudine and zidovudine

Reference	**Study treatment**	**No. of patients**	**Duration**	**Efficacy Parameters**				
				% Patients achieving viral loads <200 copies/ml	**% Patients achieving viral loads <50 copies/ml**	**% Patients achieving viral loads <20 copies/ml**	**Mean reduction in plasma HIV RNA levels log_{10} copies/ml**	Mean CD4+ cell count increase
French M et al. 2002	AZT + 3TC + NVP	22	52 weeks	NS	73 %	NS	1.29	139 (cells/μL)
	d4T + 3TC + NVP			NS	68 %	NS	2.13	113
	d4T + ddI + NVP			NS	80%	NS	1.78	174
Podzamczer D et al. 2002	AZT + 3TC + NVP	72	12 months	75%	NS	65%	NS	162*
	AZT + 3TC + Nelfinavir	70		60%	NS	50%	NS	173*

NVP = nevirapine; d4T = stavudine; 3TC= lamivudine; AZT= zidovudine; NS= not stated; *- a gain ($CD4+/mm^3$)

11. Summary of comparative evidence on safety:

Estimate of total patient exposure to date
None since the product is under development.

Description of adverse effects/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	10%	7%
Dizziness	11%	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) pediatric patients have been listed in table below.

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

Adverse Event	Lamivudine plus Zidovudine	Didanosine
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	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) pediatric 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 pediatric 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.

(Prescribing Information EPIVIR, GlaxoSmithKline, USA, Oct 2006).

Zidovudine

Adults: The frequency and severity of adverse events associated with the use of Zidovudine are greater in patients with more advanced infection at the time of initiation of therapy.

Summary of adverse events reported at a statistically significant greater incidence for patients receiving zidovudine (500 mg/day) in a monotherapy study are as follows:

Table: Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection (ACTG019).

Adverse Event	Zidovudine 500 mg/day (n=453)	Placebo (n=428)
Body as a whole		
Asthenia	8.6%*	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

*- not statistically significant versus placebo

In addition to the adverse events listed above, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Table . Frequencies of Selected Laboratory Abnormalities in Patients with Asymptomatic HIV Infection.

Adverse Event	zidovudine (500 mg/day)	Placebo
anemia (Hgb<8 g/dL)	1.1%	0.2%
granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
thrombocytopenia (platelets<50,000/mm^3)	0%	0.5%
, ALT [>5 X Upper limit of normal (ULN)]	3.1%	2.6%
AST (>5 X ULN)	0.9%	1.6%
alkaline phosphatase (>5 X ULN)	0%	0%

ULN = Upper limit of normal.

Pediatrics: 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) pediatric patients are listed below in Table.

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

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a whole:		
Fever	25%	32%
Digestive:		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	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.
ULN = Upper limit of normal.
ANC = Absolute neutrophil count

Table: Frequencies of Selected (Grade 3 /4) laboratory abnormalities in therapy-naïve (≤ 56 days of antiretroviral therapy) Paediatric Patients.

Adverse Event (Laboratory Abnormalities)	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Neutropenia (ANC<400 cells/mm^3)	8%	3%
Anemia(Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (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%

Additional adverse events reported in open-label studies in paediatric patients receiving zidovudine 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss. The clinical adverse events reported among adult recipients of zidovudine may also occur in paediatric patients.

Use for the Prevention of Maternal-Fetal Transmission of HIV: In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission, zidovudine syrup at 2

mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm^3). Anemia occurred in 22% of the neonates who received zidovudine and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving zidovudine compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during use of zidovudine in clinical practice. 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 either their seriousness, frequency of reporting, potential causal connection to zidovudine, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat.

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

(US Prescribing Information *RETROVIR,* Nov 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.

Pediatric 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).

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.

Infants who are identified as HIV infected during the first 6 weeks of life while receiving zidovudine chemoprophylaxis should have zidovudine discontinued and should be assessed to determine the need for initiation of standard combination treatment.

Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm3 or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of zidovudine, and/or blood transfusions, has occurred during treatment with zidovudine alone or in combination with other antiretrovirals.

In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction for zidovudine is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematologic toxicity.

Summary of comparative safety against comparators

No studies have been conducted. However a Comparative bioavailability study with the innovator formulations has been planned.

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

Ranbaxy's proposed FDC of LNZ = per unit cost = USD 0.116

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)***
Ranbaxy's proposed FDC of LNZ	**126**
Epivir® **+** **Retrovir ®** **+** **Viramune ®**	**82** **259 = 742** **401**
Cost Benefit/per year of treatment	**616**
* **Source:** Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries. 9th Edition, July 2006 downloaqded 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)

Product is currently under development.

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 Zidovudine plus Lamivudine plus Nevirapine.

Source: http://mednet3.who.int/EMLib/modelFormulary/modelFormulary.asp
The following is also based on Product Information for Douvir-N (a fixed combination dose of zidovudine, lamivudine and nevirapine).
(http://www.inhousepharmacy.com/hiv/duovir-n.html).

Name:

Zidovudine (Azidothymidine, AZT, ZDV)
PLUS
Lamivudine
PLUS
Nevirapine.

Composition:

Each tablet for oral suspension will contain:
Lamivudine ..... 30 mg
Zidovudine USP ..... 60 mg
Nevirapine ..... 60 mg

Use:

Zidovudine plus lamivudine plus nevirapine:

The fixed combination is indicated for the treatment of HIV infection in children. Both zidovudine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. Both drugs act by terminating the growth of the DNA chain and inhibiting the reverse transcriptase enzyme of HIV. Nevirapine is a non-nucleoside reverse transcriptase inhibitor. It acts by directly inhibiting reverse transcriptase.

Dose:

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 zidovudine 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.

The fixed dose combination should be taken by mouth twice daily, with or without food.

Patients weight (Kg)	FDC tablets to be given per dose
9.0 - 9.9	1.5
10.0 - 10.9	1.5
11.0 - 11.9	1.5
12.0 - 13.9	2
14.0 - 16.9	2
17.0 - 19.9	2.5
20.0 - 24.9	3

Contraindications:

Zidovudine plus lamivudine plus nevirapine:

The fixed combination is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the formulation. The fixed dose combination is also contraindicated for patients who are just initiating therapy with nevirapine. These patients require a lead-in dose of nevirapine, whereas this formulation contains the maintenance dose of nevirapine.

Nevirapine:

Severe hepatic impairment; post-exposure prophylaxis.

Precautions:

Zidovudine plus lamivudine plus nevirapine:

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including stavudine and lamivudine. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering zidovudine and lamivudine to any patient, and particularly to those with known risk factors for liver disease. Cases have also been reported in patients with no known risk factors. Treatment should be discontinued in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis), even in the absence of marked amino-transferase elevations.

Bone marrow suppression The fixed combination should be used in caution in patients who have bone marrow compromise evidenced by granulocyte count < 1000 cells/mm^3 or hemoglobin < 9.5 g/dl.

Myopathy

Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

Patients with HIV and hepatitis B virus coinfection

In clinical trials, some patients with HIV infection who have chronic liver disease due to hepatitis B virus infection experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine. Consequences may be more severe in patients with decompensated liver disease.

Hypersensitivity reactions

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities must discontinue nevirapine as soon as possible. Nevirapine therapy must be initiated with a 14-day lead - in period of 200 mg/day (4 mg/kg/day in paediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation and administration of the fixed dose should not occur until the rash has resolved (See Dosage and Administration).

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia), has occurred in patients treated with nevirapine. Some of these cases began in the first few weeks of therapy, and some were accompanied by rash. Nevirapine administration should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values. Nevirapine should be permanently discontinued if liver function abnormalities recur upon readministration. Monitoring of ALT and AST is strongly recommended, especially during the first six months of nevirapine treatment (See Side Effects and Dosage).

Adverse effects:

Lamivudine:

Pancreatitis has been reported with the use of lamivudine.

Lactic acidosis and hepatic steatosis, hepatitis and liver failure have been reported with the use of antiretroviral nucleoside analogs, alone or in combination. Other side effects associated with the use of lamivudine are diarrhoea, malaise and fatigue, headache, nausea and vomiting, abdominal pain and discomfort, peripheral neuropathy, arthralgias, myalgias, skin rash, pruritus, transient neutropenia and thrombocytopenia and rarely, pancreatitis. Transiently elevated levels of hepatic enzymes and bilirubin (> 5 times the normal level) have also been observed occasionally during treatment with the drug. Resolution of transient neutropenia and raised hepatic and bilirubin levels occurred without dosage modification or discontinuation of therapy.

Zidovudine;

The anaemia reported in patients with advanced HIV disease receiving zidovudine appears to be the result of impaired erythrocyte maturation. Thrombocytopenia has also been reported in patients with advanced disease. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.

Clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1,500 mg/day of zidovudine were: fever, headache, nausea, vomiting, anorexia, myalgia, insomnia, dizziness, paraesthesias, dyspnoea and rash. Malaise, gastrointestinal pain, dyspepsia and taste perversion were also reported.

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.

With respect to laboratory abnormalities, asymptomatic elevations in GGT levels are more frequent in nevirapine recipients than in controls. Because clinical hepatitis has been reported in nevirapine-treated patients, monitoring of ALT (SGPT) and AST (SGOT) is strongly recommended, especially during the first six months of nevirapine treatment (See Warnings and Precautions). Decreased neutrophils (< 750/mm3), platelets (< 50,000/mm3) and Hb (< 8.0 g/dL), and increased total bilirubin (> 2.5 mg/dL) have also been reported.

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