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Steady State Evaluation of Two Extended Release (XR) Nevirapine (NVP) Tablets 400 mg QD Compared with Immediate Release (IR) NVP Tablets 200 mg BID in HIV-1 Infected Patients

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Abstract

Background

NVP IR 200 mg BID is part of combination therapy for HIV-1 infection. Boehringer Ingelheim developed two NVP XR tablet formulations (20% and 25%) to be given QD.

Methods:

This was an international, open label, multistage, parallel group, crossover study. Patients (≤50 c/mL) who had been treated for >12 weeks with a stable regime based on IR 200 mg BID were switched to NVP XR (Group A 25%, Group B 20%) 400 mg QD for 19 days. Plasma samples at steady state after IR and XR were collected over a 24-h period.

Results

In 48 patients treated with XR, NVP was absorbed slowly (tmax 6.7 – 8.6 h vs ≤2 h for IR). The NVP Cmin of XR was comparable to that of IR while the Cmax was lower. Relative bioavailability (based on AUC0-24) of XR to IR was 80% and 71% for the 25% and 20% tablets. The incidence of AEs was low and comparable in both groups. No virologic failures were observed.

	Group A		Group B	
Parameters	XR 25%	IR	XR 20%	IR
AUC_{0-24} [g·h/mL]	82.0	103.0	101.0	137.0
C_{max} µg/mL]	4.14	5.95	4,85	7.34
C_{min} µg/mL]	2.92	3.24	3.60	4.50
t_{max} (h)	6.7	1.7	8.6	2.0
C_{max}/C_{min} ratio	1.48	1.87	1.42	1.67

Conclusions

Both NVP XR formulations were safe and well tolerated. Administration of NVP XR 400 mg QD resulted in extended absorption and reductions in peak levels at steady state while attaining similar troughs. The XR 25% formulation exhibited better bioavailability and variability than the XR 20% and was selected for further development.

Introduction

Adherence is important in preventing treatment failure and drug resistance in HIV therapy (1,2). Once daily (QD) dosing is preferred to improve compliance. Viramune® (NVP IR) 200 mg tablets are given twice daily (BID) as part of combination therapy for HIV-1 infection. Boehringer Ingelheim developed two extended release formulations of NVP (identified as XR 25% and XR 20%) to allow QD dosing as a means of improving therapy with Viramune.

This study compared the relative bioavailability at steady state of each NVP XR formulation with that of NVP IR in subjects infected with HIV-1.

Methods

This clinical trial was an international, open label, multistage, parallel group, crossover study. Eligible subjects were males and females infected with HIV-1 fully suppressed to <50 c/mL at screening who had been treated for >12 weeks with a stable regimen containing NVP IR 200 mg BID without protease inhibitors.

After entering the study, subjects continued treatment with NVP IR 200 mg BID for an additional 3 days (reference treatment). Then subjects were switched to one of the two NVP XR 400 mg QD formulations (25% or 20%) for 19 days (test treatment). Plasma samples were taken for 24 h following the last dose of each treatment.

Trial Endpoints:

- AUC_{0-24} --- to define relative bioavailability
- t_{max}, C_{max}, C_{min}, C_{max}/C_{min} ratio -- as other pharmacokinetic parameters
- Adverse events (AEs), clinical laboratory, viral load at each visit (every 3 days).

Results

Demographics

Demographic characteristics were similar in treatment groups.

Table 1. Demographic characteristics of study subjects

	Group A (XR 25%) N=24	Group B (XR 20%) N=24
Male	22 (91.7%)	21 (87.5%)
White	24 (100%)	22 (91.7%)
Age [years]*	45.2 (7.9)	44.0 (8.4)
Height [cm]*	177.3 (7.9)	176.0 (7.5)
Weight [kg]*	74.0 (11.6)	71.8 (10.5)
BMI [kg/m^2]*	23.5 (2.5)	23.2 (3.0)

*Mean (standard deviation)

Pharmacokinetics

The relative bioavailability compared with NVP IR (based on gMean ratios of AUC_{0-24}) was 80% (90% CI 73.0 - 86.7) for NVP XR 25% and 71% (90% CI 63.3 - 86.7) for NVP XR 20%. Group B (XR 20%) showed greater inter-individual variability in plasma concentrations of NVP than Group A (XR 25%).

Compared with NVP IR (Table 2), both NVP XR formulations resulted in: longer t_{max}, lower C_{max}, and similar C_{min} (89.6%)(90%CI 80.6 – 99.6) for NVP XR 25%, but lower C_{min} (75.1%) (90%CI 65.1 – 85.6)for NVP XR 20%.

NVP concentration-time profiles of both XR formulations exhibited less fluctuation than for NVP IR (Figures 1 and 2).

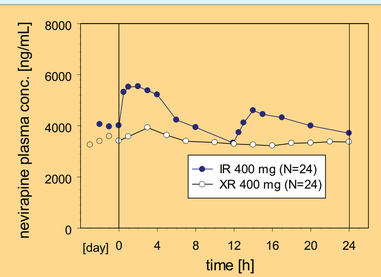

Figure 1: Plasma concentration of NVP in group A after NVP XR 400 mg 25% QD compared with NVP IR 200 mg BID

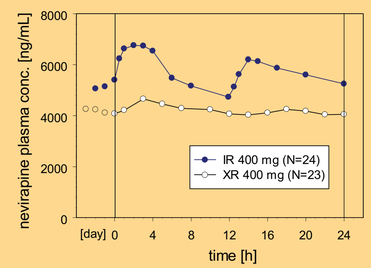

Figure 2: Plasma concentration of NVP in group B after NVP XR 400 mg 20% QD compared with NVP IR 200 mg BID

Table 2. Pharmacokinetic parameters of NVP XR compared with NVP IR

	Group A (N=24)		Group B (N=24)	
	XR 25%	IR	**XR 20%**	IR
AUC_{0-24} [ng·h/mL]*	**82000 (27)**	103000 (26)	**101000 (44)**	137000 (36)
C_{max} [ng/mL]*	**4140 (22)**	5950 (27)	**4850 (42)**	7340 (34)
C_{min} [ng/mL]*	**2920 (32)**	3240 (31)	**3600 (49)**	4500 (40)
t_{max} [h]*	**6.7 (120)**	1.7 (57)	**8.6 (98)**	2.0 (56)
C_{max}/C_{min} ratio*	**1.48 (16.4)**	1.87 (12.9)	**1.42 (16.6)**	1.67 (12.5)

*Mean (% coefficient of variation)

Safety

The frequency of patients with AEs during 19 days treatment with NVP XR was low and similar with both XR formulations (14/24 subjects with XR 25% vs 10/24 subjects with XR 20%). Adverse events were usually mild (DAIDS grade 1; 12/24 subjects with XR 25% vs 9/24 subjects with XR 20%). No subjects experienced severe or serious AEs. One subject in each group had an AE which was considered drug-related – diarrhea with XR 25% and increased HIV RNA (blip) with XR 20%. The most frequently reported AE was nasopharyngitis (0/24 subjects with XR 25% vs 4/24 with XR 20%).

No clinically relevant changes in laboratory values (including transaminase elevations) were observed. There were no virologic failures.

Conclusions

- Administration of NVP XR 400 mg QD resulted in extended absorption and reductions in peak levels at steady state while attaining similar troughs as NVP IR.
- NVP XR 25% tablets exhibited better bioavailability and lower variability than the NVP XR 20% formulation.
- Both NVP XR formulations were safe and well tolerated.
- No virologic failures were observed.

Based on these findings, NVP XR 25% was selected for further development.

References

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