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Application Number. 20-933

20-636/SE1-009

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

OCT 16 1998

NDA: 20636 (SE1-009)
20933

DRUG: Nevirapine

SPONSOR: Boehringer Ingelheim

TYPE: Pediatric supplement,
Pediatric suspension

FINAL REVIEW: 10/16/98

REVIEWER: Vanitha J. Sekar, Ph.D.

FORMULATION: 50 mg/5ml suspension

SUBMISSION DATE: March 9, 1998
April 20, 1998

LOGGED IN: 3/19/98, 5/1/98

DRAFT REVIEW: 6/15/98, 8/6/98, 8/15/98,
10/16/98

BACKGROUND: Viramune® (Nevirapine, 200 mg tablets) is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. The current recommended dose for nevirapine is 200 mg qd for the first 14 days, followed by 200 mg bid, in combination with antiretroviral agents. Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Peak plasma concentrations (2 ± 0.4 µg/ml) are attained by 4 hours following a single 200 mg dose. Following multiple doses, peak nevirapine concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. The absorption of nevirapine is not affected by the presence of food or antacids. Nevirapine is highly lipophilic and is widely distributed to tissues. It is approximately 60% bound to plasma proteins in the concentration range of . *In-vitro* and *in-vivo* studies with nevirapine suggest that it is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In-vitro* studies indicate that metabolism of nevirapine primarily occurs by the CYP3A enzymes. Elimination occurs primarily via renal excretion of glucuronidated metabolites. Nevirapine has been shown to be an inducer of cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two to four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day. The most frequently reported adverse events associated with nevirapine therapy in patients undergoing combination therapy in Phase I/II controlled trials was rash (17%). Other less frequently reported adverse events include fever, nausea, headache, and abnormal liver function tests.

Pediatric safety, pharmacokinetic and some activity data are described in this supplement (NDA 20636, SE1-009) to support the use of nevirapine in pediatric patients. The pivotal study (1100.882) includes pharmacokinetic, safety, tolerance and activity data of nevirapine alone and in double or triple combinations with nucleoside analogs. The issues of duration of exposure and larger patient numbers are being addressed by a long term open-label follow-up study 1100.892, and a comparative study ACTG 245. Additional supportive pharmacokinetic data are provided from other studies.

NDA 20933 was submitted for the approval of the suspension formulation. The pivotal bioequivalence study was 1100.1231. Additional supportive data are provided from other studies.

APPLICANT'S RATIONALE: The primary reason for developing pediatric dosing for nevirapine is the scarcity of therapeutic options available for children with HIV. In an effort to streamline the first multiple dose pediatric trials, both monotherapy and combination therapy with zidovudine (ZDV) were to be studied in a single trial (1100.882). When the emergence of reduced nevirapine sensitivity was identified in isolates from treated adult patients, the pediatric trial had included only 3 children. The trial was halted while adult data were examined and a plan developed for future trials. The pediatric trial was subsequently restarted with some adjustments in the doses based on the data available in adults. As children who entered the trial on monotherapy began to fail,

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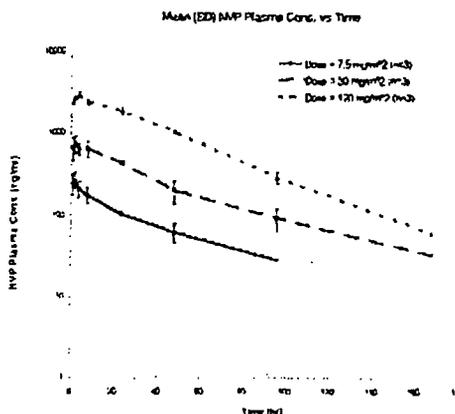
their therapy was supplemented by the addition of other drugs. As the trial continued, double therapy with ZDV and nevirapine (NVP) was introduced simultaneously in a group of children. As the trial progressed, in keeping with current clinical practices, the protocol was amended to allow for initial treatment with three drugs. Efficacy data are limited and were collected from this small cohort in the study. This application is predominantly based on safety and pharmacokinetic data to support the recommended administration of nevirapine in the pediatric population.

STUDY SUMMARIES:

A. Study 1100.853: A Single Rising Dose Pharmacokinetic Phase I Evaluation of Nevirapine Suspension by Oral Administration in Children with HIV-1 Infection

This was an open label, parallel design Phase I study in 9 HIV infected children to evaluate the tolerance and pharmacokinetics of nevirapine following single doses of a pediatric suspension. Children between the ages of 9 months and 14 years received single doses of nevirapine suspension (Lot PD.1145) at one of 3 dose levels: 7.5 mg/kg, 30 mg/kg and 120 mg/kg (n=3 per dose level).

Results: Mean plasma concentration-time profiles and mean pharmacokinetic data for the three dose levels of nevirapine suspension are shown below.



Pharmacokinetic parameters presented as Mean (SD)

Dose (mg/m ²)	Dose (mg/kg)	C _{max} (ng/ml)	T _{max} (hr)	AUC _∞ (ng/ml*hr)	t _{1/2} (hr)	CVF (ml/m ² /hr)	CVF (ml/kg/hr)
7.5 (n=3)	0.26 (0.05)	268.7 (68.2)	1.7 (0.6)	9151.3 (1687.1)	34.1 (15.4)	840.7 (172.1)	30.1 (12.5)
30 (n=3)	1.17 (0.25)	724.0 (167.8)	2.0 (0.0)	30233.7 (5912.1)	28.3 (11.6)	1017.2 (192.5)	40.6 (16.1)
120 (n=3)	4.91 (0.61)	2869 (233.1)	3.3 (1.2)	135137.3 (4214.3)	29.4 (3.6)	888.6 (28.1)	36.3 (3.5)

C_{max} and AUC_∞ increased proportionally to the doses administered. The average terminal half-life across doses was 30.6 ± 10.2 hours. Historical comparison of the single dose pharmacokinetic parameters for nevirapine suspension in HIV infected children to those in adults from another study (1100.896) was performed. The results suggest that the apparent clearance of nevirapine in children following a single dose is approximately 2 fold higher than that in adults.

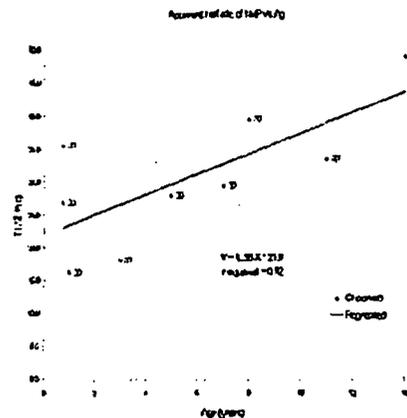
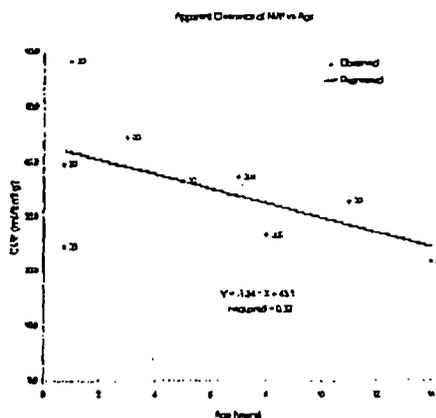
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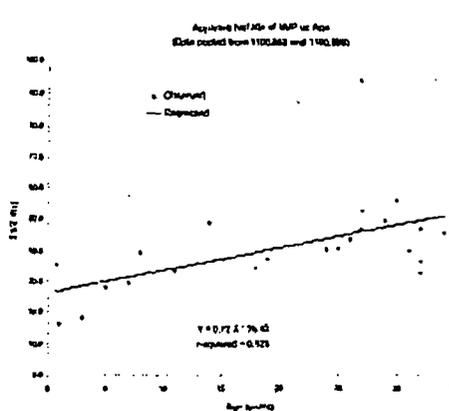
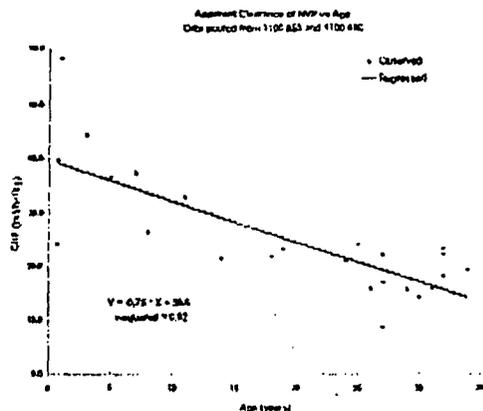
Study No.	Group	Age (years)	Dose Range	CL/F (ml/kg/hr)	T _{1/2} (hr)
1100.853	children (n=9)	0.75-14	7.5-120 mg/m ² suspension	35.7 ± 11.3	30.6 ± 10.2
1100.896	adults (n=15)	18-34	50-100 mg suspension and tablets	18.8 ± 4.0	45.3 ± 9.2

Pooling of pharmacokinetic data following suspension and tablet administration is acceptable since the applicant has demonstrated bioequivalence of the two dosage forms.

The apparent clearance and half-life for nevirapine in children appeared to be related to age, with clearance decreasing as a function of age and half-life increasing with age.



The linear equation appears to describe the data for children older than 5 years of age better than it does for children less than 5 years of age. Pooling of suspension pharmacokinetic data from the adult study (1100.896) with this pediatric study suggests that nevirapine CL/F and T_{1/2} following a single dose for children 5-14 years of age is more similar to that in adults than to the CL/F and T_{1/2} in children 0.75-5 years, following a single dose.



B. Study 1100.882: "Pharmacokinetics, Safety, Tolerance and Activity of Nevirapine Alone, In Combination with ZDV and ddI in Mildly to Moderately Symptomatic HIV-1 Infected Children."

This multiple dose study was designed to cautiously proceed from lower nevirapine doses to higher doses, monotherapy to combination therapy, and older children to younger children.

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Patients received NVP monotherapy, double therapy (NVP/ZDV), and the triple combination of nevirapine, ZDV and didanosine (ddl). According to the final amended protocol, patients were to receive nevirapine 120 mg/m² for 28 days followed by nevirapine 240 or 400 mg/m², based on age for the remainder of the study. Pharmacokinetic sampling for nevirapine included serial sampling over 24 hours and/or single measurements of trough concentrations under steady-state conditions. Pharmacokinetic analysis included 35 patients and was performed using the NONMEM program. The effect of covariates such as age, body surface area (BSA) and body weight (BW) on nevirapine clearance and volume of distribution was explored. The analysis suggested that the covariates log BSA and log BW explain the inter-individual variability in nevirapine clearance to a similar extent.

Final nevirapine PK parameters derived from log BSA (body surface area) model

Parameter	Estimate ± SE	Interpatient variability (%)
TVCL (L/hr) = $\theta_2 + \theta_4 \times \log_{10} \text{BSA}$	$\theta_2 = 2.19 \pm 0.134$ $\theta_4 = 3.17 \pm 0.267$	19.1
TVV (L) = $\theta_3 + \theta_6 \times \text{BW}$	$\theta_3 = 27.7 \pm 15.4$ $\theta_6 = 15.4 \pm 0.473$	30.5

Body surface area increased proportionally with patient age ($r^2=0.93$). Nevirapine clearance adjusted for BSA showed a nonlinear relationship with patient age. The log BSA model indicated that nevirapine clearance adjusted for BSA in infants (2.2 ± 0.5 L/m²/hr) and children older than 4 years (2.0 ± 0.5 L/m²/hr) was different from that in children between the ages of 1 and 4 years (2.7 ± 0.5 L/m²/hr). The mean values for the nevirapine terminal half-life changed with nevirapine clearance.

Final nevirapine PK parameters derived from the log BW (body weight) model

Parameter	Estimate ± SE	Interpatient variability (%)
TVCL (L/hr) = $\theta_2 + \theta_4 \times \log_{10} \text{BW}$	$\theta_2 = -1.15 \pm 0.149$ $\theta_4 = 2.27 \pm 0.182$	18.1
TVV (L) = $\theta_3 + \theta_6 \times \text{BW}$	$\theta_3 = 24.7 \pm 14.4$ $\theta_6 = 1.46 \pm 0.51$	24.3

Body weight increased proportionally with patient age ($r^2=0.86$). Nevirapine clearance adjusted for BW showed a nonlinear relationship with patient age. The log BW model indicated that nevirapine clearance adjusted for BW in infants (110 ± 23 mL/kg/hr) was similar to that in children aged 1-4 years (120 ± 22 mL/kg/hr) and children 4-8 years (102 ± 17 mL/kg/hr). This model suggested that children older than 8 years has significantly lower clearance (50 ± 10 mL/kg/hr) compared to the other 3 age groups. The nevirapine terminal half-life changed with nevirapine clearance.

The applicant submitted a graph of nevirapine apparent clearance versus age (shown on the left panel below). This graph contains more than one observed value of clearance per child. The applicant was requested to present actual clearance values by treatment day for each patient. The graph was plotted with the first observed clearance in each patient versus age (shown on the right panel below). Nevirapine apparent clearance reaches a maximum by ages 1-2 years, and then decreases with age. Nevirapine apparent clearance in children less than 8 years of age (50 - 100 mL/kg/hr) is at least 2 fold greater compared to adults.

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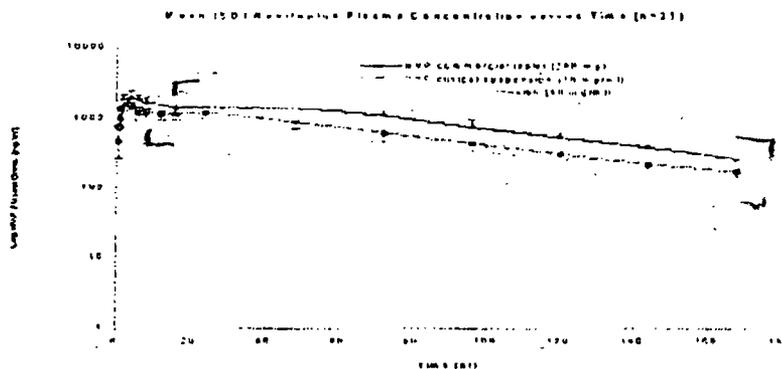
C. Study 1100.896: "An Open-Label, Randomized, 4-way, Crossover Study to Assess the Relative Bioavailability of Nevirapine in 15 Healthy Male Volunteers" (Study 1100.896) : This study was reviewed by Biopharm reviewer, Dr. Chandra Sahajwalla (Refer to NDA 20-636 Biopharm review on file in HFD 880, Division of Pharmaceutical Evaluation 3).

This was an open label, randomized, four-way crossover study (14 day washout period) in 15 healthy males (14 completed the study) to assess the relative bioavailability, pharmacokinetics and tolerance of nevirapine. Four formulations were compared: 100 mg of solution with nevirapine powder (0.25 mg/ml in _____); 100 mg suspension (5 mg/ml); and 100 mg doses of two different tablet strengths (50 mg x 2 and 100 mg x 1). The results showed that the relative bioavailability of the suspension and the two tablet formulations were all within 90% to 110% of the solution. There were no significant differences in AUC between the tablets and the solution. However, C_{max} was significantly lower and mean T_{max} higher for the suspension and two tablet formulations compared to the solution. This was a pilot study to evaluate the relative bioavailability of different nevirapine formulations for future development.

D. Study 1100.1213: "A single dose, 3-way crossover study in normal adult volunteers to assess the bioequivalence/bioavailability of nevirapine suspension (NDA batch; proposed commercial formulation) compared to nevirapine suspension (clinical batch) and nevirapine 200 mg tablets (commercial batch)."

This was a single center, open label, randomized, three way crossover single dose study in 24 healthy adult volunteers (21 completed the study) to assess the bioequivalence/bioavailability of nevirapine (pivotal study). The three study treatments were: nevirapine suspension (20 ml of 50 mg/ml, clinical batch Lot PD-1586, treatment A), nevirapine suspension (20 ml of 50 mg/5ml, NDA batch Lot PD-1714, treatment B) or 200 mg tablet (commercial batch Lot PD-1749, treatment C). There was a 2 week washout period between the three treatments.

Results: Mean plasma concentration-time profiles and mean pharmacokinetic data for the three treatments are shown below.



Pharmacokinetic parameters for the 3 study treatments

Parameter	Treatment A (clinical suspension) Mean (SD)	Treatment B (TEST) (proposed commercial suspension) Mean (SD)	Treatment C (tablet) Mean (SD)
AUC _{0-∞} (µg.h/ml)	107 (24)	106 (22)	129 (29)
C _{max} (µg/ml)	1877 (326)	1625 (283)	2097 (360)
T _{max} (hr)	3 (1)	3 (1)	5 (10)*

* Excluding Subject 9320 (T_{max} = 48 hr because the secondary peak was higher in concentration than the primary peak), the mean (SD) for T_{max} for this treatment (tablet) = 3 (2)

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90% Confidence Intervals for Log-transformed Pharmacokinetic Parameters

Computed Parameter	(Reference/Test)
	90% CI (n=17)*
$\ln AUC_{0-\infty}$	(95, 103)
$\ln C_{max}$	(82, 91)

The 90% confidence limits for C_{max} and $AUC_{0-\infty}$ passed the (0.8-1.25) criteria. These data also indicate that the T_{max} for the suspension appears to be significantly longer than that for the tablet, suggesting that the suspension may take longer to absorb relative to the tablet. However, this is not likely to be clinically significant because of the long half-life of nevirapine, and because the C_{max} is not significantly affected. The data from this study demonstrate that the suspension is bioequivalent to the commercial 200 mg nevirapine tablet.

DISSOLUTION METHOD FOR NEVIRAPINE SUSPENSION (50 mg/5 ml): The dissolution method developed for nevirapine suspension 50 mg/5 ml uses USP Apparatus II, paddles at 25 rpm, in 900 mL of 0.1 N HCl medium, with quantitation _____
 Applicant's proposed dissolution specification: Q= _____ in 45 minutes. Review of the dissolution data method suggests that the applicant's proposed method is acceptable, however the dissolution profiles support a specification of Q _____ in 45 min. This was conveyed to the applicant and was agreed upon.

CONCLUSIONS: The applicant has provided adequate information in this supplement to permit the evaluation of the pharmacokinetics of nevirapine in pediatric patients. The applicant's proposed pediatric dosing regimen is: 4 mg/kg qd for 14 days followed by 7 mg/kg b.i.d. for children 2 months to 8 years; 4 mg/kg qd for 14 days followed by 4 mg/kg b.i.d. for children older than 8 years. The doses selected are acceptable. This regimen will be reevaluated when safety data are available from study ACTG 245. The clinical trial was conducted using a dosing regimen based on body surface area using 2.5, 12.5, 50 and 100 mg nevirapine tablets (not approved) and 5 mg/ml and 10 mg/ml nevirapine suspension (NDA submitted for 10 mg/ml strength). The 10 mg/ml suspension was found to be bioequivalent to the commercially available 200 mg nevirapine tablet.

RECOMMENDATION: The pharmacokinetic studies provided as part of NDA 20636, SE1-009 provide an understanding of the pharmacokinetics of nevirapine in the pediatric population. The information submitted as part of NDA 20933 is adequate to support the approval of nevirapine suspension (50 mg/5 ml).

LABEL: A copy of the approved label is on file in the Division of Pharmaceutical Evaluation III.

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Vanitha J. Sekar, Ph.D.
Reviewer, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

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10/16/98

Concurrence: Kellie Reynolds, Pharm.D.
Acting Team Leader, Antiviral Drugs Section, DPE III
Office of Clinical Pharmacology and Biopharmaceutics

cc:	HFD-530	NDA 20636 (SE1-009)
		NDA 20933
		/MO/T.Wu
		/CSO/C. Kelly
		/Biopharm/V.Sekar
		/TL Biopharm/K.Reynolds
	HFD-340	/Viswanathan
	HFD-880	/DPEIII
	CDR	Attn: Barbara Murphy

**APPEARS THIS WAY
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A. Study 1100.853: Title: "A Single Rising Dose Pharmacokinetic Phase I Evaluation of Nevirapine Suspension by Oral Administration in Children with HIV-1 Infection."

Investigators:

Objectives: The objectives of this study were to 1) generate initial information on the pharmacokinetics and dose proportionality of nevirapine plasma levels in HIV-infected children, 2) to assess the safety and tolerance of single rising oral doses of nevirapine suspension in HIV-infected children, and 3) to confirm that the single doses which achieve trough plasma levels of approximately $10-30 \times IC_{50}$, $100-200 \times IC_{50}$ and $200-500 \times IC_{50}$ in adults achieve similar trough levels in HIV-infected children and to determine a preliminary dosing interval and dose escalation schedule for a multiple dose clinical study.

Subjects: A total of 10 subjects were screened for enrollment into the study. Nine of these subjects qualified for the study based on inclusion and exclusion criteria. Although subjects were to be 13 years or less, one subject who was 14 years old was enrolled in the study. Three subjects were assigned to each nevirapine dosage group of 7.5, 30 and 120 mg/m², respectively. All nine subjects completed the study. The demographic data are presented below.

Subj No.	Dose (mg/m ²)	Age (years)	Gender	Race	Baseline body wt (lbs)
301	7.5	14.4	M	White	113.0
302	7.5	0.7	M	Hispanic	19.4
303	7.5	3.3	M	White	31.5
304	30	7.3	F	Black	56.0
305	30	1.9	F	Hispanic	18.6
306	30	8.9	M	Hispanic	76.0
307	120	11.1	M	White	68.0
308	120	5.2	F	Hispanic	35.5
309	120	0.8	M	Hispanic	18.8

Study Design: This was an open label, parallel design Phase I study in 9 HIV infected children.

Formulations: Nevirapine suspension (25 mg/5ml) containing nevirapine (active ingredient), carbomer, polysorbate 80, sorbitol, sucrose, methylparaben, propylparaben, sodium hydroxide and water.

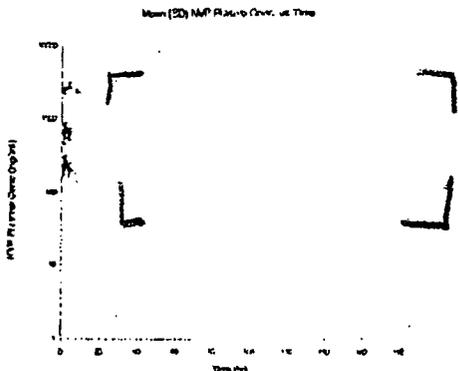
Pharmacokinetic Sampling: 2 ml blood samples were collected predose, and 1, 2, 4, 8, 24, 48, 96, and 168 hours after drug administration.

Bioanalytical Method: Plasma samples were analyzed for nevirapine concentrations using a validated method with ultraviolet detection. The applicant states that the validation studies have been previously presented in an unpublished report, DM-9208, which is listed as 'in preparation'. Since the data have not been submitted as part of this submission, the bioanalytical validation results for this study have not been reviewed.

Data Analysis: The measured plasma concentration values were used to compute the following pharmacokinetic parameters: T_{max} , C_{max} , $AUC_{0-\infty}$, $T_{1/2}$ and Cl/F . Dose proportionality plots for AUC and C_{max} were constructed. An analysis of variance (ANOVA) was performed to determine a best fit line (quadratic or linear) through the data.

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Results: The mean plasma concentration-time profile for nevirapine following a single dose suggested that peak concentrations occurred approximately 2 hours post-dose. Mean and individual pharmacokinetic parameters are shown below.



Pharmacokinetic parameters presented as Mean (SD)

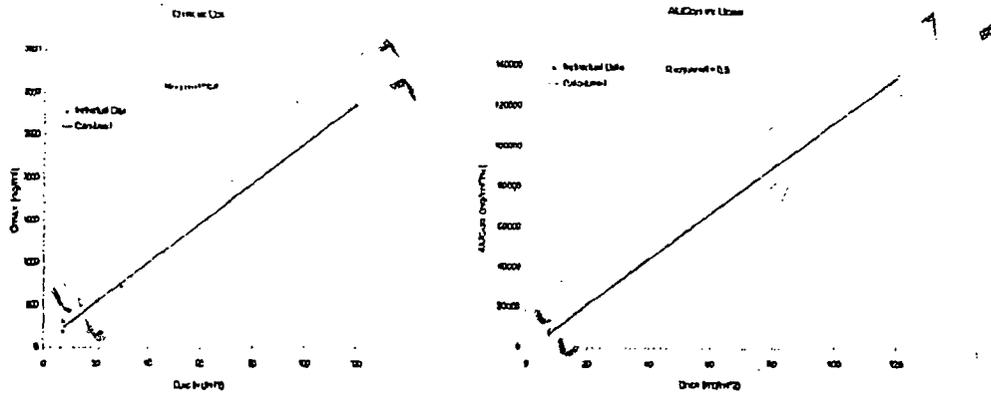
Dose (mg/m ²)	Dose (mg/kg)	C _{max} (ng/ml)	T _{max} (hr)	AUC _∞ (ng/ml*hr)	t _{1/2} (hr)	Cl/F (mg/m ² /hr)	Cl/F (mg/kg/hr)
7.5 (n=3)	0.26 (0.05)	268.7 (68.2)	1.7 (0.6)	9151.3 (1687.1)	34.1 (15.4)	840.7 (172.1)	30.1 (12.5)
30 (n=3)	1.17 (0.25)	724.0 (167.8)	2.0 (0.0)	30233.7 (5912.1)	28.3 (11.6)	1017.2 (192.5)	40.6 (16.1)
120 (n=3)	4.91 (0.61)	2869 (233.1)	3.3 (1.2)	135137.3 (4214.3)	29.4 (3.6)	888.6 (28.1)	36.3 (3.5)

Individual Nevirapine Pharmacokinetic Parameters

Subj	Age (yrs)	Dose (mg/m ²)	Dose (mg/kg)	C _{max} (ng/ml)	T _{max} (hr)	AUC _∞ (ng/ml*hr)	t _{1/2} (hr)	Cl/F (ml/m ²)	Cl/F (ml/kg)
301	14	7.5	0.26	268.7	1.7	9151.3	34.1	840.7	30.1
302	0.75								
303	3								
304	7								
305	1								
306	8								
307	11								
308	5								
309	0.75								

The data suggest that C_{max} and AUC increased proportional to dose. The doses of nevirapine used in this study corresponded to adult doses of 12.5 mg, 50 mg and 200 mg. In another adult study conducted by the applicant, in HIV-infected adults, using single doses of 12.5, 50 and 200 mg nevirapine, dose proportionality was observed in the dose-range studied. Plots of C_{max} and AUC versus dose which are shown below suggest a linear relationship between the parameters and dose. The applicant has performed an ANOVA of fitted linear and quadratic regression models to the AUC data. The applicant concludes from this analysis that this ANOVA demonstrated a preferred linear fit (p<0.0001) over the quadratic fit, suggesting dose proportionality and linear pharmacokinetics throughout this dose range. Although, an ANOVA comparing dose normalized C_{max} and AUC may have been more appropriate to analyze the data, the reviewer agrees that the data suggest dose proportionality in this dose range.

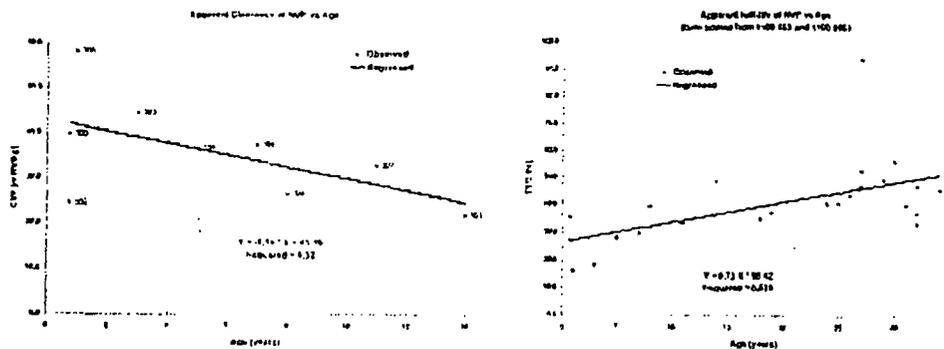
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The mean peak concentrations achieved at the 3 dose levels and their relationship to the *in-vitro* IC₅₀ against HIV-1 are shown below. Peak concentrations were achieved between 1 and 4 hours after drug administration.

Dose (mg/m ²)	C _{max} (ng/ml)	x IC ₅₀
7.5	269	25
30	753	71
120	2869	271

Results from this study suggest that the apparent clearance and half-life for nevirapine in children appear to be related to age. Clearance decreases, and half-life increases with age. Peak concentrations of nevirapine appear to be higher in younger children at each dose level.



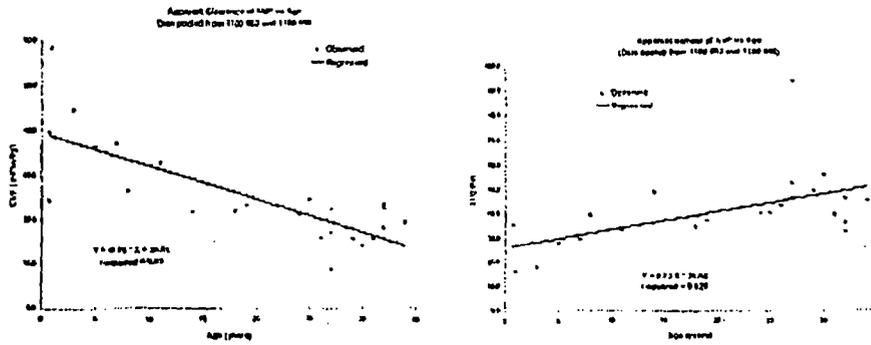
The applicant has attempted to fit the data to a linear model. For Cl/F versus age, the linear correlation appeared higher when clearance was adjusted for body weight ($r=0.57$) than when clearance was adjusted for body surface area ($r=0.3$). The correlation coefficient, r , for the linear relationship between $T_{1/2}$ and age was 0.73. Patient 302, an infant (9 months) was an exception; the infant had active hepatitis during the trial and had a lower clearance and longer $T_{1/2}$ for nevirapine compared to the other 2 children less than 1 year of age. The linear equation appears to describe the data for children older than 5 years of age better than it does for children less than 5 years of age.

The applicant has made historical comparisons of the pharmacokinetic parameters for nevirapine suspension in HIV infected children from this study to those in adults (following tablets and suspension) from another study (1100.896). The pooling of data following tablets and suspension seems reasonable since the applicant has demonstrated bioequivalence of the two formulations. This comparison suggested that the apparent clearance of nevirapine in children following a single dose appears to be approximately 2 fold higher than that in adults.

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Study No.	Group	Age (years)	Dose Range	Cl/F (ml/kg/hr)	T _{1/2} (hr)
1100.853	children (n=9)	0.75-14	7.5-120 mg/m ² suspension	35.7 ± 11.3	30.6 ± 10.2
1100.896	adults (n=15)	18-34	50-100 mg suspension and tablets	18.8 ± 4.0	45.3 ± 9.2

Pooling of suspension pharmacokinetic data from the adult study (1100.896) with this pediatric study suggests that nevirapine Cl/F and T_{1/2}, following a single dose, for children 5-14 years of age is more similar to that in adults than to the Cl/F and T_{1/2} in children 0.75-5 years.



Conclusions: The results suggest that the pharmacokinetics of nevirapine in children are different from those in adults following a single, oral dose of suspension. The disposition time of nevirapine in children is less than in adults as evidenced by a decreased AUC, increased Cl/F and shorter terminal T_{1/2} at comparable doses.

B. Study 1100.882: "Pharmacokinetics, Safety, Tolerance and Activity of Nevirapine Alone, in Combination with ZDV and ddl in Mildly to Moderately Symptomatic HIV-1 Infected Children."

Investigators: _____

Objectives: The objective of this study was to evaluate the safety, tolerance, pharmacokinetics, and activity, as determined by changes in virologic, immunologic, and growth parameters, of nevirapine alone, nevirapine in combination with zidovudine (ZDV), and the triple combination of nevirapine, ZDV and didanosine (ddl) in mildly to moderately symptomatic HIV-1 infected children between the ages of 2 months to 15 years

Subjects: Thirty seven patients were enrolled in the study: 11 subjects received only nevirapine monotherapy during the study, 17 received double therapy and 9 received triple therapy. Ten of the patients who received double therapy started out with monotherapy. The number of patients (included in the pharmacokinetic analysis) per age group was: 2 months – 2 years: 21 patients (of these 9 were < 6 months); 2-4 years: 4 patients; 4-8 years: 3 patients; 8-16 years: 7 patients.

Summary of Patients in Treatment Regimens

Treatment Regimen	Individual Patients in Regimen Group	Total Number of Patients
Monotherapy (NVP alone)	501, 541, 542, 601, 621, 622, 644, 645, 646, 1702, 1723	11
Double Therapy (NVP/ZDV)	1701, 1703, 1721, 1722, 1724, 1741, 1742, 1743, 1744, 1745, 1746, 1781, 1782, 1801, 1802, 1803, 1804	17
Triple Therapy (NVP/ZDV/ddl)	3701, 3702, 3721, 3731, 3741, 3742, 3743, 3744, 3745	9
Total		37

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Of these, 30 patients completed the study. Seven patients (601, 622, 1703, 1745, 1746, 1782, 3701) were discontinued prematurely. Two of the 7 patients discontinued due to events considered to be nevirapine-related. Thirty-five subjects were included in the population pharmacokinetic analysis. Of these, 21 subjects had serial plasma samples taken over a 24-hour sampling period. The remainder of the database was comprised of steady-state nevirapine trough concentration values (single concentration measurements). The 2 patients who were excluded from the pharmacokinetic analysis did not have any steady state plasma nevirapine concentrations that could be correlated with a known dose, regimen, body surface area and body weight on the day on which the samples were taken.

Study Design: The study was an open label, multicenter study in which patients were treated for 28 to 32 weeks, depending on their treatment regimen. The study was designed to cautiously proceed from lower nevirapine doses to higher doses, monotherapy to combination therapy, and older children to younger children. Patients received NVP monotherapy, double therapy (NVP/ZDV), and the triple combination of nevirapine, zidovudine (ZDV) and didanosine (ddi). According to the final amended protocol, patients were to receive nevirapine 120 mg/m²/day for 28 days, followed by nevirapine 240 or 400 mg/m², based on age, for the remainder of the study. (Patients ≤9 years of age received 200 mg/m²/bid and those >9 years received 120 mg/m²/bid).

Formulations: Nevirapine was supplied by BIPI in both a suspension and tablet formulation. The suspension formulation of nevirapine was supplied at a concentration of 5 mg/ml and 10 mg/ml. Nevirapine tablets were provided in strengths _____

_____ Thirty three patients received nevirapine suspension: 22 received only the to-be-marketed 10 mg/ml strength, 7 received only the 5 mg/ml strength (found to be bioequivalent to the 10 mg/ml strength) and 4 received both strengths. One of these patients also received tablets. Four patients received only nevirapine tablets.

Pharmacokinetic Sampling: Blood samples (5 ml) were collected for determination of plasma nevirapine concentrations, either over 24 hours (serial sampling) or as single measurements (trough concentrations), under steady-state conditions.

Bioanalytical Method: Plasma samples were analyzed for nevirapine concentrations at Boehringer Ingelheim Pharmaceuticals Inc. using a validated _____ with ultraviolet detection. The analytical method has been described in the reports U93-0662 and U95-3353. The limit of quantitation for the assay _____ Linearity over the range of _____ was indicated by the mean correlation coefficient of 0.9998 obtained from twenty-nine standard curves over twenty-nine days of analysis. The slopes of the standard curves had a coefficient of variation of 5.39%. Over the 29 days of analysis, the precision was better than or equal to _____ and accuracy was _____ ml quality controls, respectively.

Data Analysis: The pharmacokinetic database included patient demographics (age, weight, height) and information on nevirapine dosing. The purpose of the pharmacokinetic analysis was to derive a model that would be adequately predictive of nevirapine apparent clearance in the pediatric population. Nevirapine steady-state plasma concentration-time data were fitted by a one compartment pharmacokinetic model with first order absorption and elimination using NONMEM. The absorption rate constant k_a was fixed at 0.693 hr⁻¹, based on an observed t_{max} of approximately 2 hours following a single dose of nevirapine. Nevirapine apparent clearance (CL) and volume of distribution (Vd) were modeled by adjusting for patient demographics. Interindividual variability in CL and Vd were modeled using an exponential error model according to the following relationship: $CL_i = TVCL \times \exp(\eta^{CL})$ and $Vd_i = TVV \times \exp(\eta^{Vd})$ where,

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CL_j and Vd_j are clearance and volume of distribution for the j th patient, $TVCL$ and TVV are the typical values of clearance and volume of distribution for the study population and η represents a random error term for interpatient variability.

For model building purposes, the following criteria were used to evaluate goodness-of-fit: a) minimization of the objective function (MOF), b) minimization of the standard errors of the parameter estimates, theta, c) randomness of the scatter in plots of residuals versus Y and weighted residuals versus Y , d) minimization of the interpatient variability (omega), and e) minimization in residual variability (sigma).

Results: The simplest model, called the base model ($CL=\theta$), was compared with various models incorporating body surface area, body weight and age either as linear or log functions. These data have been submitted as part of the study report. The applicant also tried power and exponential functions using the above covariates, but these data have not been submitted. The applicant has attempted to include age as a covariate in the model as a linear function ($TVCL=\theta_2+\theta_4 \times \log_{10}Age$) and has concluded that age was not a significant covariate. However, the relationship of nevirapine clearance and age is nonlinear in nature. Therefore, the reason that age was not found to be a significant covariate maybe due to model misspecification. The applicant has not submitted any data for age as a covariate using any other models.

The analysis suggested that the covariates, log BSA and log BW explain the inter-individual variability in nevirapine clearance to a similar extent. Utilizing body surface area as the fixed effect, the final model for nevirapine clearance and volume of distribution lowered the estimate of interpatient variability from 50% to 19% compared to the base model. Similarly, utilizing body weight as the fixed effect, the final model for nevirapine clearance and volume of distribution lowered the estimate of interpatient variability from 50% to 18% compared to the base model. Utilizing body surface area and body weight as the fixed effect(s) also lowered the objective function significantly compared to the base model. Examination of the randomness of the scatter in plots of residuals versus Y and weighted residuals versus Y suggested that the logBSA and log BW models are reasonable in explaining the variability associated with nevirapine clearance.

Final nevirapine PK parameters derived from the Base model

Parameter	Estimate \pm SE	Interpatient variability (%)
$TVCL (L/hr) = \theta_2$	$\theta_2 = 1.2 \pm 0.132$	50.1
$TVV (L) = \theta_3$	$\theta_3 = 68.1 \pm 40.0$	120.4

Final nevirapine PK parameters derived from log BSA (body surface area) model

Parameter	Estimate \pm SE	Interpatient variability (%)
$TVCL (L/hr) = \theta_2 + \theta_4 \times \log_{10} BSA$	$\theta_2 = 2.19 \pm 0.134$ $\theta_4 = 3.17 \pm 0.267$	19.1
$TVV (L) = \theta_3 + \theta_5 \times BW$	$\theta_3 = 27.7 \pm 15.4$ $\theta_5 = 15.4 \pm 0.473$	30.5

Final nevirapine PK parameters derived from the log BW (body weight) model

Parameter	Estimate \pm SE	Interpatient variability (%)
$TVCL (L/hr) = \theta_2 + \theta_4 \times \log_{10} BW$	$\theta_2 = -1.15 \pm 0.149$ $\theta_4 = 2.27 \pm 0.182$	18.1
$TVV (L) = \theta_3 + \theta_5 \times BW$	$\theta_3 = 24.7 \pm 14.4$ $\theta_5 = 1.46 \pm 0.51$	24.3

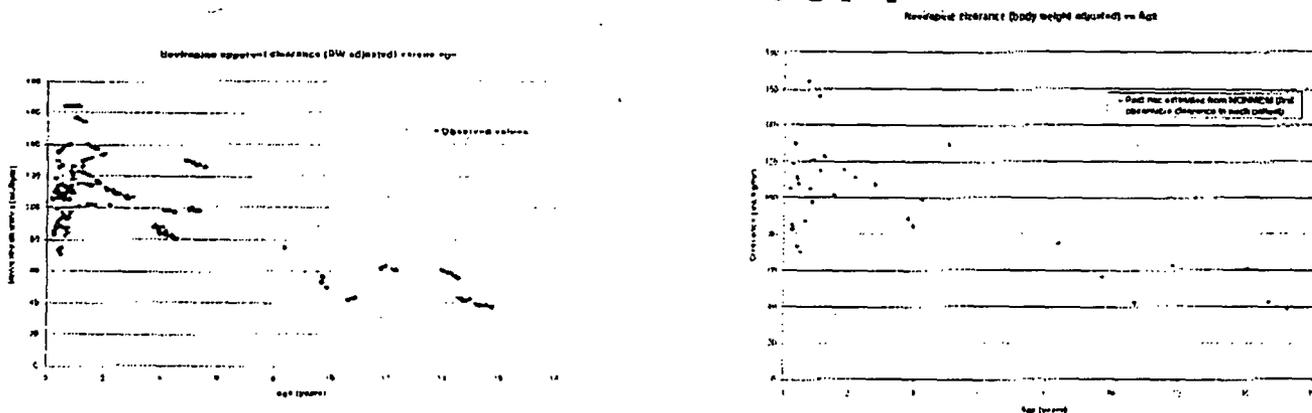
Body surface area increased proportionally with patient age ($r^2=0.93$). Nevirapine clearance adjusted for BSA showed a nonlinear relationship with patient age. The log BSA model indicated that nevirapine clearance adjusted for BSA in infants ($2.2 \pm 0.5 L/m^2/hr$) and children older than 4 years ($2.0 \pm 0.5 L/m^2/hr$) was different from that in children between the ages of 1 and 4 years ($2.7 \pm 0.5 L/m^2/hr$). The mean values for the nevirapine terminal half-life changed with nevirapine clearance. The mean half-life in infants was 34.1 hr, in children 1-4 years was 21.5 hr and in children older than 4 years was 23.8 hrs.

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Body weight increased proportionally with patient age ($r^2=0.86$). Nevirapine clearance adjusted for BW showed a nonlinear relationship with patient age (see figures below). The log BW model indicated that nevirapine clearance adjusted for BW in infants (110 ± 23 mL/kg/hr) was similar to that in children aged 1-4 years (120 ± 22 mL/kg/hr) and children 4-8 years (102 ± 17 mL/kg/hr). This model suggested that children older than 8 years has significantly lower clearance (50 ± 10 mL/kg/hr) compared to the other 3 age groups. The nevirapine terminal half-life changed with nevirapine clearance.

The applicant has submitted a graph of nevirapine apparent clearance versus age (shown on the left panel below). This graph contains more than one observable value of clearance per child. The applicant was requested to present actual clearance values by treatment day for each patient. The graph was plotted with the first observable clearance in each patient versus age (shown on the right panel below). Nevirapine apparent clearance reaches a maximum by ages 1-2 years, and then decreases with age. Nevirapine apparent clearance in children less than 8 years of age is at least 2 fold greater compared to adults.

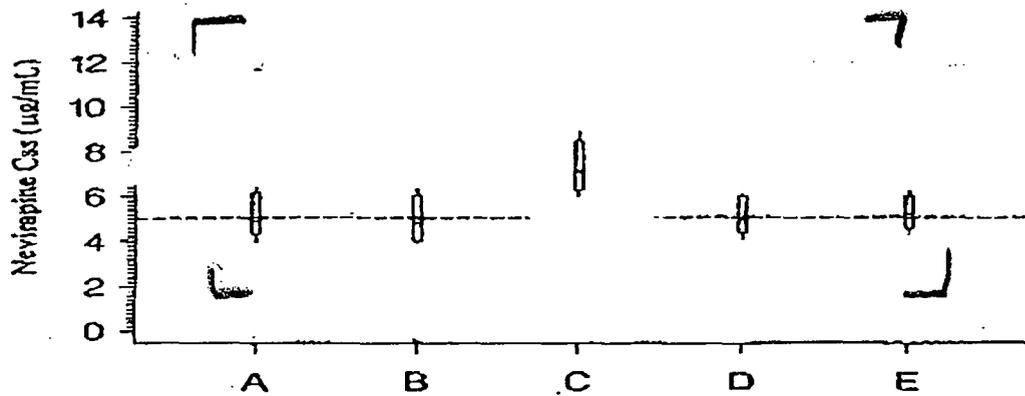
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The applicant's proposed dosing regimen is: 4 mg/kg qd for 14 days followed by 7 mg/kg bid for children 2 months to 8 years; 4 mg/kg qd for 14 days followed by 4 mg/kg bid for children older than 8 years. In support of their proposed pediatric dosing regimen, the applicant has compared average nevirapine steady state concentrations (C_{ss}) in adults to those predicted in children. The average C_{ss} in adults taking nevirapine 200 mg bid was 5.5 ± 2.2 μ g/ml. The applicant has made predictions of average C_{ss} in children using dosing regimens adjusted for body weight, because of the convenience of the use of body weight as opposed to body surface area. The applicant's proposed conversion of the dosing regimen (from BSA to body weight adjusted) seems to be reasonable. However, it should be noted that the current experience with nevirapine administration is based only on body surface area. A dose of 7 mg/kg if age <8 years, 4 mg/kg if age \geq 8 years results in C_{ss} values equivalent to the dosing regimen of 120 mg/m² bid for age \geq 8 years and 150 mg/m² bid for age <8 years. This relationship suggests that the average C_{ss} in children will range from 3–8 μ g/ml, using the proposed dosing regimens.

Note: The applicant states that the observed clearance values in the plots were obtained from single trough concentrations for some subjects and from serial plasma sampling for others. It was not clear as to how clearance estimates were obtained from single trough concentrations. The applicant indicated that post-hoc estimates from NONMEM were used.

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Nevirapine Average Steady-State Plasma Levels Observed in Adults (A) and Predicted in Pediatric Patients Utilizing Four Different Regimens (B-E)

- A) Adult Patients: Dose = 200 mg b.i.d. (Study Nos. 1100.1009, 1100.1203 and 1100.1204; n=65).
- B) Pediatric: Dose = 120 mg/m² b.i.d., not to exceed 200 mg (Study 1100.1102; all subjects, n=35).
- C) Pediatric: Dose = 200 mg/m² if age < 2 years and 120 mg/m² if age > 2 years b.i.d., not to exceed 200 mg (Study 1100.1102; all subjects, n=35).
- D) Pediatric: Dose = 6 mg/kg if age < 8 years and 4 mg/kg if age > 8 years b.i.d., not to exceed 200 mg (Study 1100.1102; all subjects, n=35).
- E) Pediatric: Dose = 4 mg/kg if age < 1 year, 7.5 mg/kg if age between 1-2 years, 6 mg/kg if age between 2-8 years and 4 mg/kg if age > 8 years b.i.d., not to exceed 200 mg (Study 1100.1102; all subjects, n=35).

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Treatment C: nevirapine 200 mg tablet (commercial batch Lot PD-1749).

There was a 2 week washout period between the three treatments. All doses were taken in a fasted state.

Pharmacokinetic Sampling: 5 ml blood samples were drawn for nevirapine analysis predose, and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 hours following each dose.

SUBJECT DEMOGRAPHICS FOR STUDY 1100.1213

PTNO	AGE	WGT	HGT	GENDER
9301	24	139	70	MALE
9302	49	144	63	FEMALE
9303	48	165	88	MALE
9304	34	178	71	MALE
9305	42	148	68	MALE
9306	31	168	88	FEMALE
9307	34	134	67	MALE
9309	36	171	67	FEMALE
9310	19	172	71	MALE
9311	49	154	65	FEMALE
9312	37	139	63	FEMALE
9313	49	163	68	MALE
9314	23	154	71	MALE
9315	33	144	62	FEMALE
9318	47	122	59	FEMALE
9318	41	128	63	FEMALE
9320	41	171	70	MALE
9321	45	138	65	FEMALE
9322	35	136	65	FEMALE
9323	43	175	89	MALE
9324	49	134	55	MALE

Bioanalytical Method: Plasma samples were analyzed for nevirapine concentrations at Boehringer Ingelheim Pharmaceuticals Inc. using a validated with ultraviolet detection. The analytical method has been described in the reports U93-0662 and U95-3353. The limit of quantitation for the assay was . Linearity over the range of was indicated by the mean correlation coefficient of 0.9999 obtained from nine standard curves over nine days of analysis. The slopes of the standard curves had a coefficient of variation of 3.12%. The precision was better than or equal to and accuracy was , respectively.

Data Analysis: The measured plasma concentration values were used to compute the following pharmacokinetic parameters: T_{max} , C_{max} , AUC_{0-168} and $AUC_{0-\infty}$. The computed parameters were analyzed using analysis of variance for a crossover design. Terms in the model were sequence, subject within sequence, period and treatment. Confidence intervals for log transformed $AUC_{0-\infty}$, C_{max} and T_{max} were determined. Treatment B was the test and was compared to treatment A and treatment C. Statistical analyses were done using SAS procedure PROC GLM.

Results: The computed mean pharmacokinetic parameters are presented below. Mean plasma nevirapine concentrations are plotted below. There was a statistically significant treatment effect for the log transformed C_{max} and $AUC_{0-\infty}$. Tests for multiple comparisons showed that for: 1) $AUC_{0-\infty}$, treatment B (test, NDA suspension) was different from treatment C (commercial tablet), and 2) C_{max} , treatment B (test, NDA suspension) was different from treatment C (commercial tablet) as well as from treatment A (clinical suspension). A statistically significant difference between sequences was also observed for these two variables; this is probably not clinically significant.

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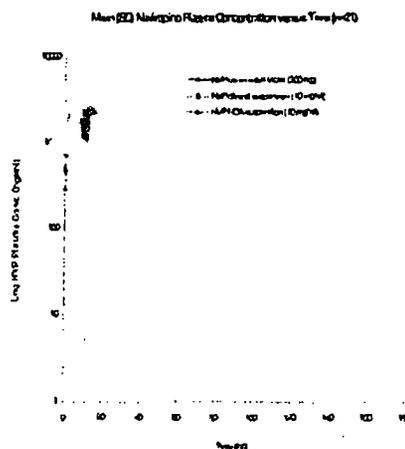
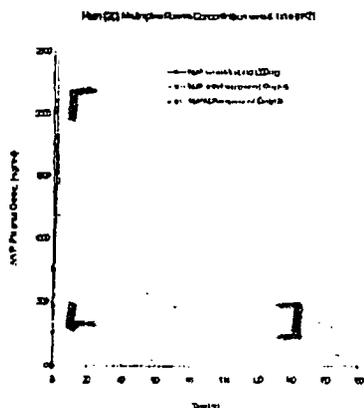
Mean Nevirapine Pharmacokinetic Parameters

Parameter	Treatment A (clinical suspension) Mean (SD)	Treatment B (TEST) (NDA suspension) Mean (SD)	Treatment C (tablet) Mean (SD)
AUC _{0-∞} (µg.h/ml)	107 (24)	106 (22)	129 (29)
C _{max} (µg/ml)	1677 (326)	1625 (283)	2097 (360)
T _{max} (hr)	3 (1)	3 (1)	5 (10)*

* Excluding Subject 9320 (t_{max} =48 hr because the secondary peak was higher in concentration than the primary peak), the mean (SD) for t_{max} for this treatment (tablet) = 3 (2)

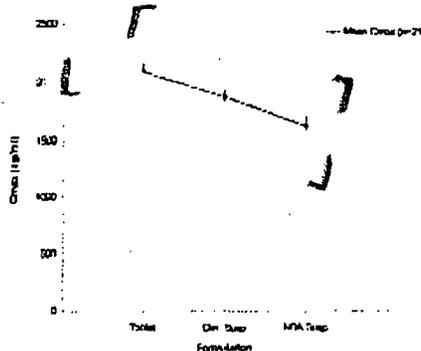
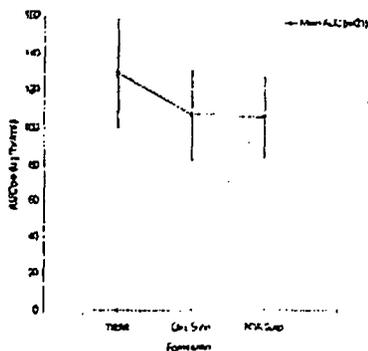
Nevirapine (Mean ± SD) Conc vs Time
(Linear, n=21)

Nevirapine (Mean ± SD) Conc vs Time
Log (n=21)



Nevirapine AUC_(0-∞) following the 3 treatments (n=21)

Nevirapine C_{max} following the 3 treatments (n=21)



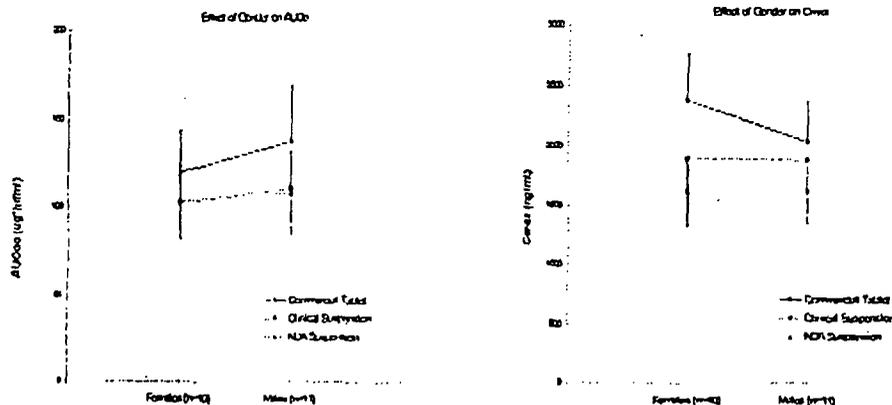
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Pharmacokinetic Parameters for individual subjects

PTNO	GENDER	Tablet (C)		Clin Susp (A)		NDA Susp (B)		Tablet (C)		Clin Susp (A)		NDA Susp (B)	
		AUC (ug/ml*hr)	AUC (ug/ml*hr)	AUC (ug/ml*hr)	C _{max} (ng/ml)	C _{max} (ng/ml)	C _{max} (ng/ml)	T _{max} (hr)					
9302	FEMALE												
9306	FEMALE												
9309	FEMALE												
9311	FEMALE												
9312	FEMALE												
9315	FEMALE												
9316	FEMALE												
9318	FEMALE												
9321	FEMALE												
9322	FEMALE												
9301	MALE												
9303	MALE												
9304	MALE												
9305	MALE												
9307	MALE												
8310	MALE												
9313	MALE												
9314	MALE												
9320	MALE												
9323	MALE												

The effect of gender on (mean) C_{max} and AUC_{0-∞} was evaluated. From these profiles (which are shown below), gender does not appear to affect the pharmacokinetics of nevirapine suspension(s) or tablet.

Effect of Gender on Nevirapine AUC_{0-∞} and C_{max}



90% confidence intervals were computed using two one-sided t-tests. The confidence intervals for AUC_{0-∞}, C_{max} and T_{max} are listed in below.

Computed Parameter	Clin Susp/Tablet (A/C)	NDA Susp/Tablet (B/C)	NDA Susp/Clin Susp (B/A)
lnAUC _{0-∞}	(81, 86): Pass (on low side)	(79, 87): Fail	(93, 103): Pass
lnC _{max}	(83, 95): Pass (on low side)	(73, 83): Fail	(81, 93): Pass (on low side)

Conclusion: The data from this study suggest that the NDA batch suspension (20 ml of 50 mg/5 ml, Lot PD-1714) has comparable bioavailability to the clinical batch nevirapine suspension (50 mg/5ml, Lot PD-1586). However, the batch of NDA suspension has a lower a bioavailability compared to the commercial tablet. The sponsor attributes this to the mode of administration of

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the suspension () and states that this contributed to the lack of a dose equivalence. The sponsor recommends that the:

Note: Since the NDA suspension (50 mg/ml) was shown to have a lower bioavailability compared to the commercial 200 mg tablet in this study (Study 1213), the sponsor carried out a second bioavailability study (Study 1231) comparing a 50 mg/5ml NDA batch suspension to the commercial tablet (reviewed below). Nevirapine suspension plasma concentration from this study (1213) and study 1231 are compared at the end of this report as mean plasma concentration-time profiles.

D. Study 1100.1231: Title: "A single dose, 2 way crossover study in normal adult volunteers to assess the bioavailability of nevirapine suspension (Lot PD-1713R) relative to commercial nevirapine tablets (Lot NS-857A)."

Investigator and Study Center: _____

Objective: The objective of this study was to assess the bioavailability of nevirapine suspension (Lot PD-1713R) relative to commercial nevirapine 200 mg tablet (Lot NS-857 A).

Subjects: Eighteen healthy male (8) and female (10) subjects, 19 to 48 years of age completed the study. The pharmacokinetic analyses were performed using all of these 18 subjects as well as using only 17 of the subjects. The concentrations of nevirapine following administration of the 200 mg tablet were very low (<100 ng/ml) in Subject 10001. The applicant also makes this observation, but does not provide any explanation for this. The demographic data are shown.

Subj No.	Age	Sex	Race	Weight (kg)
10001	37	M	White	61.7
10002	36	F	White	55.3
10003	35	F	White	66.2
10004	48	F	White	55.3
10005	37	M	White	77.5
10006	35	M	White	99.3
10007	34	M	White	78.0
10008	34	M	White	70.7
10009	41	F	White	61.2
10010	31	F	Black	61.2
10012	42	F	White	79.8
10013	46	M	White	83.4
10014	45	F	White	65.3
10015	37	F	White	80.3
10016	30	M	White	75.3
10017	38	F	White	59.4
10018	28	F	White	83.4
10021	42	M	Black	78.5

Study Design: This was a single center, open label, randomized, two way crossover single dose study. Subjects were randomized to receive nevirapine suspension (20 ml of 50 mg/ml) (Treatment A) or 200 mg tablet (Treatment B), to be followed 3 weeks later by the opposite treatment. All doses were taken in a fasted state.

Formulations: Nevirapine suspension (50 mg/5ml; NDA Batch PD-1713R) was _____ This was the test product. The ingredients in the suspension are not listed by the sponsor in this study report. Subjects were administered the

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suspension using a dosing syringe to ensure that the dose was delivered completely. Nevirapine 200 mg tablets (commercial batch, NS-857A) were used as the reference.

Pharmacokinetic Sampling: 5 ml blood samples were drawn for nevirapine analysis predose, and 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 hours following each dose.

Bioanalytical Method: Plasma samples were analyzed for nevirapine concentrations at Boehringer Ingelheim Pharmaceuticals Inc. using a _____ with ultraviolet detection. The analytical method has been described in the reports U93-0662 and U95-3353. The limit of quantitation for the assay was _____. Linearity over the range of _____ was indicated by the mean correlation coefficient of 0.9998 obtained from nine standard curves over nine days of analysis. The slopes of the standard curves had a coefficient of variation of 2.91%. The precision was better than or equal to _____ and accuracy was _____.

Data Analysis: The measured plasma concentration values were used to compute the following pharmacokinetic parameters: T_{max} , C_{max} , and AUC_{0-168} and $AUC_{0-\infty}$. The computed parameters were analyzed using analysis of variance for a crossover design. Terms in the model were sequence, subject within sequence, period and treatment. Confidence intervals for log transformed $AUC_{0-\infty}$, C_{max} , and T_{max} were determined. Treatment B (200 mg capsules) was the reference and Treatment A (20 ml of 50 mg/5 ml suspension) was the test. Statistical analyses were done using SAS procedure PROC GLM.

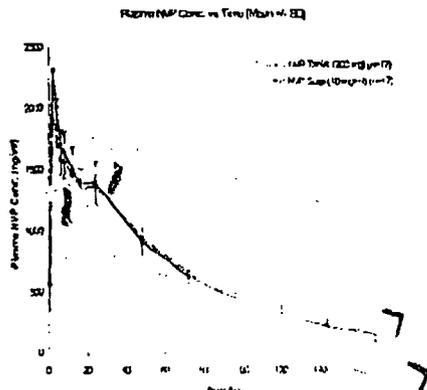
Results: The computed mean pharmacokinetic parameters are presented below. Mean plasma nevirapine concentrations are plotted below. There was no significant treatment effect for any of the pharmacokinetic parameters, except for T_{max} ($p = 0.0031$). (These analyses were performed using $n=18$ as well as $n=17$, and the same result was observed in both cases.) The mean plots that are in this review are plotted using $n=17$.

Mean Nevirapine Pharmacokinetic Parameters

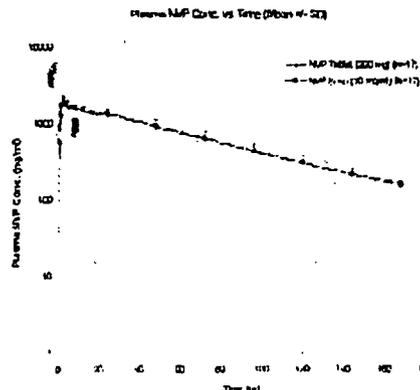
Parameter	Treatment A (suspension) Mean (SD)		Treatment A (tablet) Mean (SD)	
	n = 18	n = 17*	n = 18	n = 17*
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	127 (29)	128 (29)	123 (31)	130 (31)
C_{max} ($\mu\text{g}/\text{ml}$)	2046 (377)	2021 (377)	2224 (491)	2351 (491)
T_{max} (hr)	3 (1)	3 (1)	2 (1)	2 (1)

* Excluding Subject 10001

Nevirapine (Mean \pm SD) Conc vs Time (Linear)

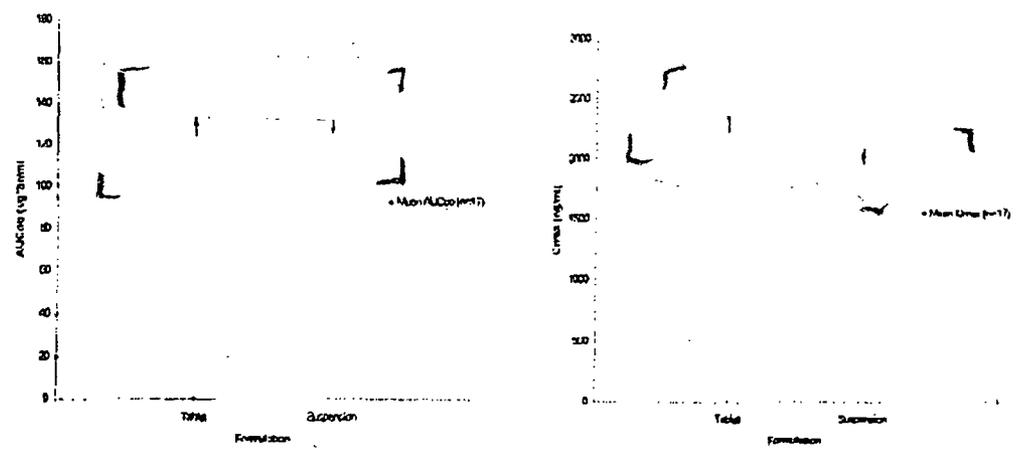


Nevirapine (Mean \pm SD) Conc vs Time (Log)



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Nevirapine AUC_{0-∞} and C_{max} for Reference (Tablet) & Test (Suspension)



The pharmacokinetic parameters (AUC_{0-∞}, C_{max} and T_{max}) for each of the subjects for both treatments are shown below. Note: The C_{max} observed in Subject 1 after tablet administration was approximately 50 fold lower than that observed in other subjects.

Pharmacokinetic Parameters for individual subjects for both treatments

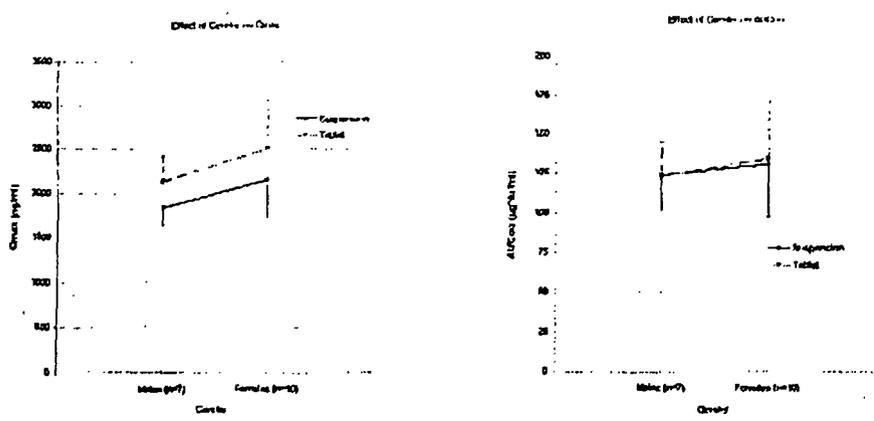
Subj	Tablet C _{max} (ng/ml)	Suspension C _{max} (ng/ml)	Tablet T _{max} (hr)	Suspension T _{max} (hr)	Tablet AUC _{0-∞} (ug*hr/ml)	Suspension AUC _{0-∞} (ug*hr/ml)
10001			1	4		
10002			2	4		
10003	T		2	2		
10004			1	2		
10005			2	4		
10006			2	4		
10007			4	4		
10008			2	6		
10009			2	1		
10010			2	2		
10012			2	4		
10013			2	2		
10014			2	2		
10015			1	2		
10016	L		2	4		
10017			2	2	L	
10018			2	4		
10021			2	2		

The effect of gender on (mean) C_{max} and AUC_{0-∞} was evaluated. From these profiles (which are shown below), gender does not appear to affect the pharmacokinetics of nevirapine suspension or tablet. 90% confidence intervals were computed using two one-sided t-tests. The confidence intervals for AUC_{0-∞}, C_{max} and T_{max} are listed in the table below.

Computed Parameter	(Reference/Test) (n=18)	(Reference/Test) (n=17)*
lnAUC _{0-∞}	(87, 222)	(95, 103)
lnC _{max}	(78, 167)	(82, 91)
T _{max}	(129, 186)	(121, 175)

* Excluding Subject 1

Effect of Gender on Nevirapine C_{max} and AUC_{0-∞}

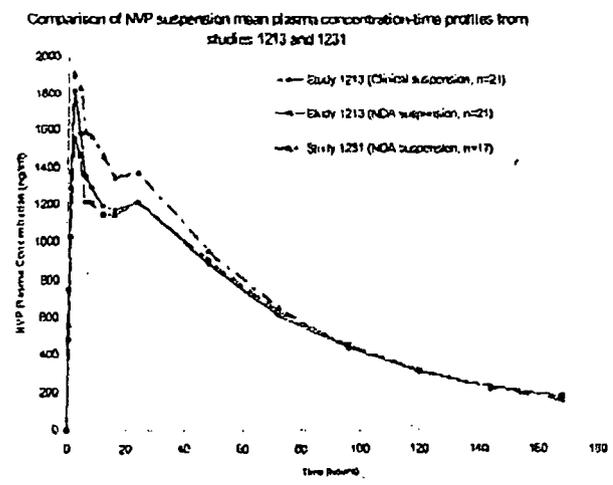


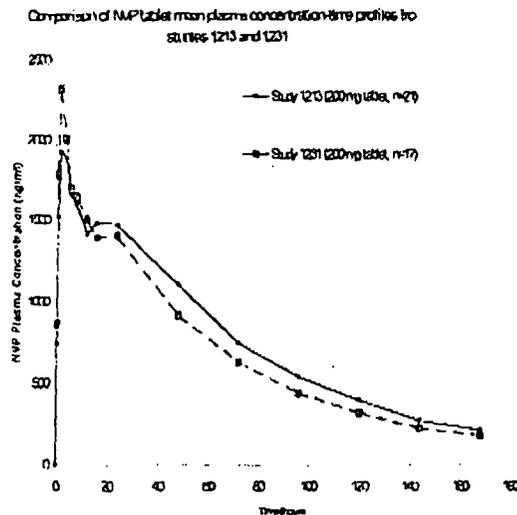
The 90% confidence limits for C_{max} and AUC_{0-∞} were outside of the (0.8-1.25) goal post when Subject 10001 was included in the analyses. However, when Subject 10001 was excluded, the 90% confidence limits for C_{max} and AUC_{0-∞} passed the (0.8-1.25) criteria. These data also indicate that the T_{max} for the suspension appears to be significantly longer than that for the tablet, suggesting that the suspension may take longer to absorb relative to the tablet. However, this is not clinically significant because of the long half-life of nevirapine, and because the C_{max} is not significantly affected.

Conclusion: The data from this study demonstrate that the suspension (20 ml of 50 mg/5 ml) is bioequivalent to the commercial 200 mg nevirapine tablet.

A comparison of the suspension and tablet pharmacokinetic data was made between the two bioequivalence studies, 1213 and 1231. The profiles suggest that the plasma concentrations following the suspension appear to be higher in the second study (1231) compared to the first study (1213) in which the NDA batch suspension was shown to have comparable bioavailability to the commercial tablet. The exposure following the commercial tablet

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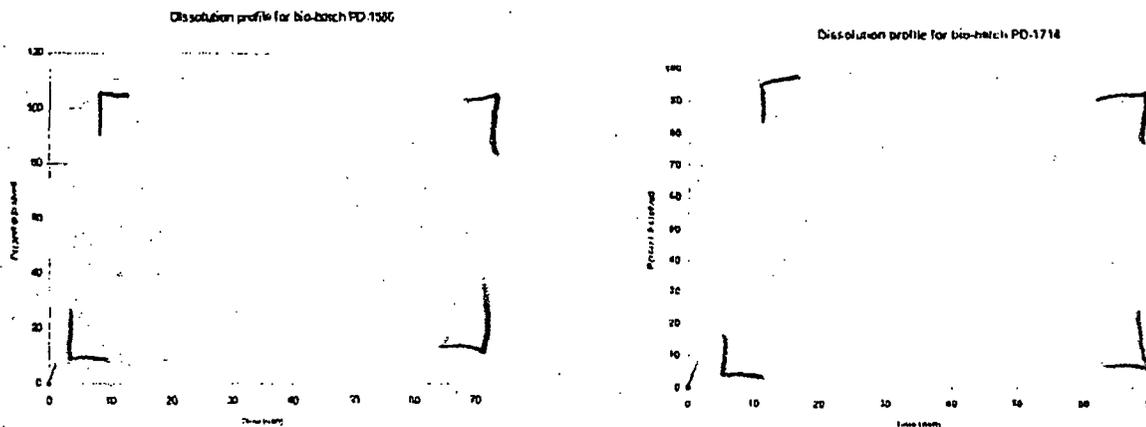




appears to be similar across studies. In study 1213, the batch of NDA suspension has a lower a bioavailability compared to the commercial tablet. The applicant attributes this to the mode of administration of the suspension (30 cc cups were used and the suspension following administration). The applicant states that this contributed to lower plasma concentrations of the suspension compared to the tablet and to the lack of a dose equivalence. The above profiles comparing suspension and tablet plasma concentration-time profiles between the two studies implies that the applicant's explanation is rational.

DISSOLUTION METHOD FOR NEVIRAPINE SUSPENSION (50mg/5ml): The dissolution method developed for nevirapine suspension 50 mg/5 ml uses USP Apparatus II, paddles at 25 rpm, in 900 mL of 0.1 N HCl medium, with . This method was tested for robustness by evaluating the effects of different paddle speeds (20, 25, 30 rpm), temperatures (35°C, 37°C, 39°C) and media concentration (0.1 N HCl, 0.09 N HCl, 0.11 N HCl) on the dissolution profile. The results suggested that small changes in paddle speed, temperature and media concentration do not affect the dissolution profile of nevirapine suspension. Applicant's proposed dissolution specification: Q= 45 minutes.

Dissolution data for nevirapine suspension batches used in bioequivalence study 1100.1213.



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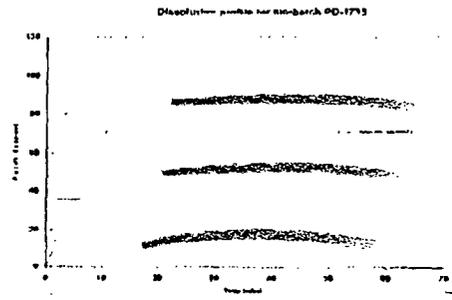
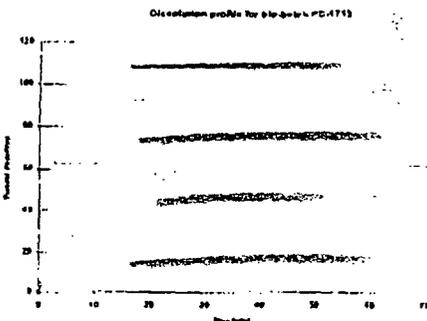
Batch #	Batch size	Date of manufacture
PD-1714	_____	Oct-96
PD-1586	_____	Jan-96

Batch PD-1586

Time (min)	Percent dissolved						Mean	SD
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
0	0	0	0	0	0	0	0	0.0
15	7							7
30	7							7
45	7							7
60	7							7

Batch PD-1714

Time (min)	Percent dissolved						Mean	SD
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
0	0	0	0	0	0	0	0	0.0
15	7							7
30	7							7
45	7							7
60	7							7



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Dissolution data for primary stability batches

Batch # 1713

Time (min)	Percent dissolved						Mean	SD
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
0	0	0	0	0	0	0	0	0.0
15								
30								
45								
60								

Batch # 1715

Time (min)	Percent dissolved						Mean	SD
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6		
0	0	0	0	0	0	0	0	0.0
15								
30								
45								
60								

Review of the dissolution data method suggests that the applicant's proposed method is acceptable, however the dissolution profiles support a specification of Q: ~~45~~ 45 min. This was conveyed to the applicant and agreed upon.

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