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APPLICATION NUMBER:

20-636 /S-017

20-933 /S-007

MEDICAL REVIEW

NDA 20-636 / SE-017
NDA 20-933 / SE-07

Medical Officer's Review

Date Submitted: May 31, 2001
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Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Drug: Chemical: 5,11-dihydro-11-cyclopropyl-4-methyl-6H-
dipyrido-[3,2-b:3'-e][1,4]diazepin-6-one

Generic: Nevirapine
Trade: VIRAMUNE®

Route: Oral

Dosage Form: 200 mg tablets and 10 mg/mL suspension

Proposed Indication: Treatment of HIV-1 infection in combination with
other antiretroviral agents

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1. Resume

The applicant has requested traditional approval for VIRAMUNE® (nevirapine tablets), a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents. This indication is based on virologic response in controlled studies through 48 weeks in duration.

In support of the request for traditional approval, the applicant has submitted the 48-week surrogate endpoints and safety data from one large adequate and well-controlled trial. In addition, the applicant has submitted 48-week surrogate endpoint and safety data from two smaller controlled studies, and safety experience from two other phase 2/3 studies.

The principal controlled study, BI 1090, in combination with the two supportive studies, Atlantic study and INCAS provide adequate evidence that nevirapine in combination with other antiretroviral agents has an effect on surrogate endpoints over 48 weeks that are reasonably likely to be associated with clinical benefit. The primary efficacy measure in Study 1090 was proportion of patients with HIV RNA levels < 50 copies/ml at 48 weeks of therapy.

Study BI 1090 was an international, double blind, randomized, placebo-controlled study to evaluate the tolerance, safety, and effectiveness of nevirapine in 2,249 adult patients with < 200 CD4+ cells at screening. The trial was initiated in December 1995, conducted in 176 clinical sites, and was completed in August 1998. The study compared treatment with nevirapine (NVP) + lamivudine (LAM) + background therapy (B) versus placebo (P) + LAM + background therapy in NNRTI-naive patients. The nevirapine dose was 200 mg daily for two weeks followed by 200 mg twice daily or placebo. Nineteen percent of patients in NVP/LAM/B arm and 3% of patients in the P/LAM/B arm achieved HIV RNA < 50 copies/ml at week 48 of therapy. The on-treatment change in baseline in CD4 count through 48 weeks was significantly greater for the NVP group compared to the placebo group. The time to first new CDC AIDS-defining event or death was improved in event-free survival in the NVP group compared to the placebo group.

One of the supportive studies, Atlantic (BI 1229), was a randomized, open-label study designed to evaluate the safety and efficacy of three different drug combination therapies in 298 anti-retroviral naïve patients with > 200 CD4+ cells/mm³ at entry. The study was conducted in Europe and North America and compared groups including an NNRTI (NVP), a protease-inhibitor (indinavir - IDV) or a NRTI (LAM), all in combination with two other NRTIs (didanosine - ddI and stavudine - d4T). The nevirapine doses were 200 mg daily for two weeks followed by 400 mg once daily. Fifty-eight percent of patient in the NVP treatment arm compared to 57% in the IDV arm and to 59% in the LAM arm achieved HIV RNA < 500 copies/ml at week 48 of treatment. There was no significant difference in the mean CD4 cell counts among the treatment arms.

The second supportive trial, INCAS (BI 1046), was a randomized, placebo-controlled, double-blinded multinational trial conducted in Italy, the Netherlands, Canada, and

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Australia. The study compared the virologic and immunologic activity of three treatment groups at 48 weeks in 151 antiretroviral naïve patients with >200 CD4 cells/ml at entry. The treatment arms were NVP + ddi + zidovudine (ZDV), NVP + ddi placebo + ZDV, and NVP placebo + ddi + ZDV. The nevirapine doses were 200 mg daily for two weeks followed by 200 mg twice daily or placebo. Forty-five percent of patients treated with NVP/ddi/ZDV achieved HIV RNA < 400 copies/ml at 48 weeks compared to 19% for ddi/ZDV and 0% for NVP/ZDV.

The safety database consists of data from the three studies mentioned above (BI 1090, Atlantic, and INCAS) and two additional placebo-controlled trials, BI 1037 and BI 1038. A safety update was submitted on September 24, 2001 as an amendment to the NDA.

Trials BI 1037 and 1038 were double-blind, randomized, 52 week trials to evaluate the safety and effectiveness of nevirapine in HIV-infected patients who had CD4 counts > 200 cells/ml. The study populations in these two trials consisted predominantly of antiretroviral naïve, AIDS-free patients. The treatment arms for BI 1037 were NVP + ZDV and ZDV alone in 60 patients. The treatment arms for BI 1038 were NVP + ZDV, NVP alone, ZDV alone, or dual placebo in 245 patients. Treatment doses of NVP in the trials were 200 mg daily for 2 weeks followed by 200 mg twice daily. After six months of blinded therapy in studies BI 1037 and BI 1038, patients were offered open-label nevirapine therapy. Among the 150 placebo-treated patients in those two studies, 121 (81%) chose open-label nevirapine

A total of 3,003 patients were enrolled in the five studies presented in the NDA. A total of 1,463 patients received nevirapine as initial therapy. The following table lists the number of patients who received study drugs in each of the studies.

Table 1. List of controlled studies discussed in NDA and number of treated patients in each

Study	Received NVP	Received control regimen	Total receiving treatment
BI 1090	1,121	1,128	2,249
BI 1229 (Atlantic)	89	209	298
BI 1046 (INCAS)	98	53	151
BI 1037	30	30	60
BI 1038	125	120	245
Total	1,463	1,540	3,003

The most notable adverse events associated with nevirapine therapy were hepatotoxicity and skin rash.

Serious hepatic adverse events, including hepatic failure, hepatitis, cholestatic hepatitis, and infectious hepatitis, were more common in nevirapine-treated patients (53/1374 or

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3.9%) compared to placebo (23/1331 or 1.7%). Serious hepatic adverse events also included patients presenting with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase level. Hepatitis and related hepatic events continue to occur throughout nevirapine treatment. Patients with signs or symptoms of hepatitis must immediately seek medical evaluation, have liver function tests performed, and be advised to discontinue nevirapine as soon as possible.

Rash was the most common adverse event reported; 23% (316/1374) of patients treated with nevirapine and 14% (186/1331) control patients developed rash. The nevirapine associated rash occurred frequently [63% (200/316)] in the first six weeks of therapy, but also occurred at later times. Severe rashes with blistering, desquamation, or ulceration were reported in 23/316 (7.2%) of nevirapine-treated patients with rash compared to 4/186 (2.2%) of control patients with rash; one nevirapine-treated patient developed Stevens-Johnson Syndrome as did one placebo-treated patient, the latter was attributed to trimethoprim-sulfa.

The data in this application support the conclusion that nevirapine in combination with other antiretroviral agents is safe and effective for the treatment of HIV-1 infection.

2. Regulatory history

Boehringer Ingelheim Pharmaceuticals, Inc. submitted the IND for nevirapine on December 26, 1990. The first phase 1 clinical trials commenced in January 1991. Controlled clinical trials with surrogate marker endpoints were initiated in February 1993. The applicant met with the FDA for an End of Phase 2 meeting on February 6, 1995, which led to a closed session with the Division of Antiviral Drug Products (DAVDP) Advisory Committee on April 4, 1995 to discuss adequacy of overall drug development. The applicant returned to FDA for a Pre-NDA meeting on August 7, 1995. The NDA for accelerated approval was submitted on February 23, 1996. On June 7, 1996, the applicant met with the DAVDP Advisory Committee in open session. On June 21, 1996, FDA granted accelerated approval for nevirapine. The applicant submitted a supplemental NDA package for traditional approval on December 23, 1997, which was withdrawn in June 1998. A supplemental NDA package for nevirapine solution in pediatric patients was submitted June 1998 and approved September 1998 that provided dosing recommendations for infants and children greater than 2 months of age. Following several teleconferences with the Division in ensuing months, this revised NDA package for traditional approval was submitted on May 31, 2001.

3. Summary of NDA clinical section

The clinical section of this application includes the study reports of three phase 3 clinical trials, and safety reports from two additional trials in adults.

4. Phase 3 clinical trials

The review of the application included an evaluation of the analyses presented by the applicant and construction of safety and efficacy tables from the electronic database on all patients in the principal studies. This review also included an examination of case report forms and patient narratives for deaths and patients with serious hepatotoxicity and selected patients with other adverse events.

A. BI 1090 (starts at volume 40)

Title: An international double-blind, randomized, phase 3 study to evaluate the tolerance, safety, and effectiveness of VIRAMUNE® (nevirapine) in preventing clinical AIDS progression events or death when used in combination with lamivudine (3TC) and background antiviral therapy.

Objective: The study was designed to demonstrate clinical benefit of nevirapine in patients with advanced disease (CD4 count less than 200 cells/mm³ at screening). However, it was modified after the study was completed and sought to examine the effect of nevirapine treatment compared with placebo, when used in conjunction with lamivudine plus additional antiretroviral therapy, on the sustained suppression of plasma HIV RNA, i.e., the proportion of patients who had suppression at 48 weeks.

Design: This randomized, double blind study was designed to evaluate the safety and efficacy of NVP compared to placebo. In addition, all patients received 3TC and additional antiretroviral therapy selected by the investigator. Antiretroviral-naïve patients were to receive at least one background agent on day 0. Antiretroviral-experience patients continued their background antiretroviral therapy or had the option to switch their background agents on day 0. Originally, protease inhibitors (PIs) were prohibited as part of the background therapy; this changed to allow PIs (Amendment 5, February 1997). Patients assigned to NVP treatment received a lead-in dose of 200 mg/day for 2 weeks, followed by 200-mg bid. All patients received 3TC 150-mg bid and background therapy at doses determined by the prescribing physician. Patients were to be seen at day 14, every month for 4 months, then every 2 months thereafter until 18 months after the last patient enrolled or 24 months, whichever came first. Once a patient experienced an AIDS defining event, blinded study drug was discontinued, and patients were eligible for open-label NVP. Patients, who stopped study drug or left the study prior to Amendment 5 for various reasons, including prohibition of PIs, were offered the opportunity to restart blinded medications. Patients, who had permanently discontinued from the study, were to be contacted to reconsent and restart blinded medication, receive open-label medications, or have minimal follow-up for the rest of the study. Plasma samples were to be collected from all patients and stored for later viral load testing. A Data Safety Monitoring Board monitored the trial.

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Endpoints: The primary endpoint was proportion of patients with HIV PCR (Roche Amplicor Ultra Sensitive test) below 50 copies/ml at 48 weeks using an intent to treat analysis, non-completers equals failure. The co-primary analysis compared the time to first confirmed new CDC Category C event or death.

Study Population: Two thousand two hundred fifty six (2256) patients were enrolled and randomized, 2249 received study therapy and were included in analyses. Demographic characteristics for the patients included 968 (43%) from Europe, 575 (26%) from North America, 524 (23%) from South Africa, and 182 (8%) from South America. The median age for all patients was 36.5 years. Seventy-nine percent (79%) were male, 70% were Caucasian. One thousand fifteen (45%) had a prior CDC category C event, 248 (11%) were antiretroviral-therapy naïve. The average baseline CD4 count (average of CD4 count on day 0 and second CD4 count at visit 1) was 107 cells/mm³. The median baseline HIV RNA levels were 43,650 copies/ml for NVP-treated patients and 33,110 copies for placebo-treated patients. At baseline, 451 patients (20%) were seropositive for HCV antibodies, 199 (9%) were HBsAg-positive; 410 (18%) patients had ever used or were currently using illicit IV drugs. Source: Table 11.2.1:1 Volume 52, page 73.

Prior therapy: Of the 2,249 patients, there were 248 (11%) who were naïve to antiretroviral therapy; 279 (12%) who had received only zidovudine therapy.

Table 2. Initial background therapy at start of double-blind therapy

	NVP (n=1121)	Placebo (n=1128)
Two NRTIs	580 (52)	610 (54)
More than two NRTIs	444 (40)	411 (36)
NRTIs and PIs	97 (9)	107 (10)

Note: All patients received lamivudine as part of initial therapy.

Table 12.1.1:1, volume 52, page 101

Table 3. Outcomes through 48 weeks

Outcome	NVP-treated (N=1121) %	Placebo-treated (N=1128) %
Success at 48 weeks: Viral load < 50 copies/ml and no clinical failure	18.0	1.6
Treatment failure	82.0	98.4
Never less than 50 copies/ml.	44.6	66.4
Confirmed rebound	7.2	4.3
CDC category C event	9.6	11.2
Added new antiretroviral therapy while < 50 copies/ml	5.0	0.9
Discontinued due to AE	7.0	5.9
Discontinued for other reason	8.5	9.8

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Note: Virologic success was reported as HIV RNA < 50 copies/ml.

Source: The statistical reviewers analysis, Table 2.6.1 B on page 5 of his draft review – a modification on Table 11.4.1.1:2 (Vol. 40, page 44), see Appendix 16.1.92, STATDOC 6.1.18 of NDA submission).

Table 4. Subset analysis: HIV RNA < 50 copies/ml at week 48 by disease, antiretroviral treatment history and other baseline characteristics

	NVP – % responders (number of responders / number in group)	Placebo - % responders (number of responders / number in group)
Prior CDC stage C event	13% (67/510)	1% (4/505)
No prior CDC C event	22% (133/611)	2 % (15/623)
Treatment naïve	39% (46/117)	0% (0/131)
ZDV alone	12% (108/873)	2% (18/849)
Other prior therapy	35% (46/131)	1% (1/148)
Baseline CD4 count		
< 25 cells/ml.	7% (13/194)	1% (1/181)
25 – 50	9% (12/140)	4% (6/139)
50 – 100	14% (38/269)	2% (4/255)
> 100 cells/ml.	26% (137/518)	1% (8/553)
Baseline HIV RNA		
< 5,000 copies/ml	29% (54/188)	5% (11/222)
5,000 – 100,000	16% (91/565)	1% (5/578)
> 100,000 copies/ml	16% (55/349)	1% (2/311)
Total	18% (200/1121)	2% 19/1128)

Source Table 11.4.1.1:1, Volume 40, page 77. Modified by Statistical reviewer, Table 3.4A.

Table 5. Additional subset analyses by statistical reviewer: HIV RNA < 50 copies/ml at week 48 by baseline characteristics

	NVP - % responders (number of responders / number in group)	Placebo - % responders (number of responders / number in group)
Male	16% (143/879)	2% (14/902)
Female	24% (57/242)	2% (5/226)
Age in years		
17 – 33	17% (56/339)	1% (3/337)
33 – 41	17% (76/458)	2% (11/447)
41 – 72	21% (68/324)	1% (5/344)
Race		
White	17% (140/816)	2% (14/835)
Black	19% (52/277)	2% (5/264)
Other	29% (8/28)	0% (0/29)
Residence		
Europe	15% (71/480)	2% (10/488)
North America	10% (30/286)	2% (6/289)

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South Africa	30% (79/263)	0% (1/261)
South America	22% (20/92)	2% (2/90)

Source: Table 3.4, Statistical review, page 15.

Co-primary clinical endpoints

Table 6. First HIV Clinical Progression Event or Death, according to treatment group

	NVP-treated (N=1121)	Placebo-treated (N=1128)
Patients with Clinical Progression Event	144 (13%)	169 (15%)
Deaths, Total	80 (7)	89 (8)
Clinical Progression Event (not death)	89 (8)	116 (10)
Deaths as First Event	55 (5)	53 (5)

Source: Table 11.4.1.2. (vol. 40, page 86). See appendix 16.1.9.2, STATDOC 6.2.1.1.1 and STATDOC 6.2.3.1.

There appears to be no significant difference in the rates of HIV clinical progression by study treatment for the analysis presented by the sponsor (See Note below).

Table 7. Most frequently occurring category C events according to treatment group

Event	NVP-treated (N=1121)	Placebo-treated (N=1128)
Total, first clinical progression event (not death)	89	116
Presumed PCP	5	11
Confirmed PCP	6	6
CMV retinitis	12	10
MAI, disseminated or extrapulmonary	13	9
CNS toxoplasmosis	6	7
Presumed esophageal candidiasis	4	9
PML	2	9
Cryptococcosis – extrapulmonary	5	6
HIV wasting syndrome	3	7
Other	33	42

Source: Table 11.4.1.2 (vol. 40, page 87), See Table 14.2.2.1

Cox regression analysis was performed, which examined baseline characteristics, treatment group and prior antiretroviral therapy, to determine factors that influenced time to failure. Although statistically insignificant ($p=0.07$), the sponsor's analysis demonstrated a trend favoring NVP therapy. Note: Dr. Hammerstom, DAVDP statistical reviewer, re-analyzed clinical progression using Kaplan-Meier analysis and concludes

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that there is clinical benefit. At two year into the study, 16% on nevirapine had experienced class C CDC events as compared to 21% of subjects on the control arm.

The change from baseline in CD4 count through one year of therapy was significantly greater for the nevirapine group compared to placebo. The following table shows the mean CD4 counts in trial 1090 at baseline, 6 months and one year for patients continued on study by treatment group.

Table 8. Immunologic parameters by treatment group.

	NVP group - Mean CD4 count (No. patients)	Placebo group - Mean CD4 count (No. patients)
Baseline	106 (1121)	110 (1128)
6 months	168 (885)	137 (870)
One year	207 (816)	167 (776)

Source: Modified from Dr. Hammerstrom's analysis (Statistical reviewer).

As initially designed the primary endpoint of Trial 1090 was time to first CDC event. The sponsor concluded that there was no statistically significant difference between the arms and that the trial failed to demonstrate clinical efficacy of nevirapine. The FDA statistical reviewer re-analyzed clinical progression using Kaplan-Meier analysis and concluded that there was clinical benefit. At two year into the study, 16% on nevirapine had experienced class C CDC events as compared to 21% of subjects on the control arm. In the past for clinical endpoint studies, FDA did not count missing data as failures, as evaluated in the sponsor's primary analysis. The FDA analysis suggests that there is clinical benefit to the inclusion of nevirapine in an antiretroviral regimen and that is due to longer periods of viral suppression for the nevirapine-treated patients.

Evaluation of Safety

There were 107 deaths during the double blind period of the study; 49 (4%) in the NVP group and 58 (5%) in the placebo group. Narratives for 170 deaths are submitted; 88 in the NVP group and 82 in the placebo group. In general, the deaths reflect predominantly AIDS-defining illnesses, wasting, other cancers and rarely, suicide.

Disposition of subjects: Of 2,256 randomized patients, seven did not receive therapy and were not included in the analysis. About half the patients discontinued double-blind therapy prematurely, half completed the study.

The following table depicts the reasons for premature discontinuations.

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Table 9. Patient Disposition – Subjects discontinued from double-blind medication

Disposition	NVP N (%)	Placebo N (%)	Total N (%)
Randomized and treated	1,121 (100)	1,128 (100)	2,249 (100)
Prematurely discontinued	524 (47)	614 (54)	1,138 (51)
Adverse event:	205 (18)	188 (17)	393 (17)
Drug-related AE	110 (10)	77 (7)	187 (8)
Confirmed AIDS	72 (6)	83 (7)	155 (7)
Progression			
Unexpected worsening of disease	23 (2)	28 (2)	51 (2)
Lack of efficacy	165 (15)	238 (21)	403 (18)
Administrative*	101 (9)	121 (11)	222 (10)
Other	53 (5)	67 (6)	120 (5)
Patients Completed	597 (53)	514 (46)	1,111 (49)

Administrative reasons included loss to follow-up, noncompliance, and withdrawal of consent. Source: Table 10.1:2 (volume 52, page 69).

Table 10. Selected new onset adverse events with onset during the double-blind period

Adverse event	NVP (N=1121)	Placebo (N=1128)
Diarrhea	194 (17)	264 (23)
Rash*	268 (24)	165 (15)
Moniliasis	200 (18)	232 (21)
URI	206 (18)	193 (17)
Nausea	183 (16)	192 (17)
Headache	167 (15)	153 (14)
Fever	155 (14)	154 (14)
Pain	139 (12)	167 (15)
Coughing	125 (11)	117 (10)
Bronchitis	120 (11)	122 (11)
Herpes simplex	121 (11)	117 (10)
Vomiting	120 (11)	102 (9)
Abdominal pain	88 (8)	125 (11)
Fatigue	96 (9)	105 (9)
Granulocytopenia	91 (8)	103 (9)
Hepatic events†	104 (9)	84 (7)
Abnormal LFTs‡	63 (6)	57 (5)
Peripheral neuropathy	58 (5)	54 (5)
Anemia	54 (5)	58 (5)
Depression	52 (5)	55 (5)
GI disorder (not specified)	42 (4)	37 (3)
Increased amylase	26 (2)	34 (3)

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*Rash includes rash, allergic reaction with rash, erythematous rash, maculopapular rash, pustular rash, SJS, and urticaria

† Hepatic events include hepatitis, cholestatic hepatitis, infectious hepatitis, hepatic failure, abnormal hepatic function, hepatocellular damage, hepatomegaly, hepatorenal syndrome, hepatosplenomegaly, jaundice, increased LDH, fatty liver, LFTs abnormal, bilirubinemia, bilirubinuria, hepatic coma, hepatic necrosis, hepatic infarction, cirrhosis.

‡ Increased LFTs: From baseline to maximum value on blinded medication, an increase of either SGOT or SGPT to \geq grade 3 (5 x ULN) or increase to 2x baseline if baseline was \geq 1.25 x ULN, or increase to 2 x ULN if baseline < 1.25 x ULN.

Source: Table 12.2.2 and 12.2.2.2; vol. 52, pages 104-5, 113-4.

Rash was the most common adverse event observed among nevirapine-treated patients. Rash was observed in 268 or 24 % of nevirapine treated patients compared to 165 (15%) of controls. The sponsor provided a summary of rash observed during blinded therapy. For the additional analysis, the sponsor excluded 15 of 268 (6%) of the nevirapine-associated rashes and 8 of 165 (5%) of the rashes in the control group because those rashes were attributed to specific "clearly-identified" diagnoses, i.e., viral exanthemas, scabies, contact dermatitis, folliculitis, or isolated pruritus.

The following table provides a summary of rash observed during blinded treatment.

Table 11.

	NVP group (N=1121)	Placebo Group (N=1128)
Patients with rash	253 (23%)	158 (14%)
Intensity of rash		
Mild	156 (62%)	113 (72%)
Moderate	79 (31)	44 (28)
Severe	18 (7)	1 (1)
Patients who permanently discontinued blinded medication with rash	51 (5% of patients) (20% of patients with rash)	15 (1% of patients) (9.5% of patients with rash)
Severity of rash		
Grade 1	96 (38%)	78 (49%)
Grade 2	127 (50)	70 (44)
Grade 3	30 (12)	10 (6)
Grade 4	0	0

Note: Rashes are graded as follows: Grade 1 – erythema, pruritis; Grade 2 – diffuse, no constitutional findings, or urticarial rash; Grade 3 – rash with constitutional findings; and Grade 4 – rash with skin detachment covering >10%.

Source: Table 12.2.2.1:1, volume 52, page 107.

One patient developed Stevens-Johnson syndrome in the NVP-treated group and one in the placebo group.

Nevirapine treatment was associated with increased risk for clinical hepatic events; 104 (9%) of patients treated with nevirapine compared to 84 (7%) of control patients. There was less evidence of increased risk of elevated LFTs attributable to nevirapine. The

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strongest and most consistent risk factors for clinical hepatic events in study 1090 were chronic HBV and HCV infections and any elevation of SGOT or SGPT at baseline; both for NVP and placebo-treated patients. A more thorough discussion of risk factors for hepatic events and rash can be found in Part 5 of this report – Integrated Summary of Safety - in which combined data from study BI 1090, 1037, 1038, and 1046 are included.

Summary Conclusions of Study BI 1090

The results of Study BI 1090 support nevirapine as safe and effective therapy in combination with other antiretroviral therapies for HIV-1 infection. With 2,249 patients, 1,121 treated with nevirapine, Study BI 1090 was the principal study powered to compare nevirapine + lamivudine + background therapy compared with nevirapine placebo + lamivudine + background therapy in HIV-1 patients with advanced disease. Almost 90% of enrolled patients had received prior therapy with monotherapy or dual therapy prior to entering the trial. In addition, 45% of participants had previously experienced an AIDS-defining clinical event prior to entry. The study arms appeared to be well balanced with respect to baseline and demographic variables. Eighteen percent of patients in the NVP-treated arm and 1.6% in the control arm achieved HIV RNA < 50 copies/ml at 48 weeks of therapy. The change from baseline in CD4+ cell count through one year of therapy was significantly greater for the nevirapine group. The results of this study suggest that nevirapine in combination with other antiretroviral agents is efficacious.

Rash was observed in approximately one-quarter of patients treated with nevirapine, commonly presenting during the first 6 weeks of therapy and resulted in discontinuation of nevirapine in approximately 5% of patients. Clinical hepatic events were observed in 9% of nevirapine-treated patients compared to 7% of those treated with placebo.

B. Atlantic Study (BI 1229) – (starts with volume 59)

Title: A randomized, open-label study to evaluate the efficacy and safety of three triple-combination therapies aimed at different HIV targets in antiretroviral naïve HIV-1 infected patients.

Objective: To compare the relative effects of three different triple drug therapy approaches on HIV-1 replication:

- Triple NRTI therapy
- HIV protease inhibitor plus two NRTI therapy
- NNRTI plus two NRTI therapy.

Study Design: This was a phase 3 randomized, multicenter, open-label study conducted in Europe and North America by the International Antiviral Treatment Center (IATEC) based in the Netherlands. The treatment arms were as follows:

1. Nevirapine 200 mg qd for 14 days, then nevirapine 400 mg qd + stavudine 40 mg bid (30 mg bid if body weight < 60 kg) + didanosine 400 mg qd (N=89)

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2. Indinavir 800 mg q8h + stavudine 40 mg bid (30 mg bid if body weight < 60 kg) + didanosine 400 mg qd (N=100)
3. Lamivudine 150 mg bid + stavudine 40 mg bid (30 mg bid if body weight < 60 kg) + didanosine 400 mg qd (N=109).

Outcome measures: The primary endpoint is the proportion of patients with HIV-1 RNA less than 500 copies/ml at 48 weeks.

Study Population: Two-hundred-ninety-eight antiretroviral naïve patients with asymptomatic HIV infection, HIV RNA \geq 500 copies/ml and CD4+ T-cell count \geq 200/ml were enrolled. Patients were excluded with the following laboratory values during screening: Hemoglobin less than 7 mmol/l (< 6.5 for women), absolute neutrophil count < 750/ml, thrombocyte count < 25,000/ml, ALT/AST \geq 5 X ULN, or serum creatinine > 1.5 x ULN. Demographic characteristics for the patients included 70% from Europe, 30% from North America. The median age for all patients was 35.5 years. Eighty percent were male; 92% were CDC stage A, 7% stage B, and 1% stage C. The median CD4 count was 406 cells/ μ l, median log₁₀ HIV-1 RNA 4.25, 12.8 % of subjects had baseline HIV-1 RNA > 100,000 copies/ml. Source: Table 11.2.1, Vol. 60, page 48.

Efficacy results

Table 12. Proportion of subjects HIV-RNA < 500 copies/ml at 48 weeks, intention-to-treat analysis

Treatment group	Proportion < 500 copies/ml at 48 weeks (%)	Confidence intervals, 95%
NVP-d4T-ddI	52/89 (58)	(48.2-68.7)
IDV-d4T-ddI	57/100 (57)	(47.3-66.7)
3TC-d4T-ddI	64/109 (59)	(49.5-68.0)

Source: Table 11.4.4, vol. 60, page 51

Mean CD4 counts increased for all three treatment groups during the study. There were no significant differences between treatment groups with respect to initial immunologic response or sustained response (Source: Volume 60, page 78). The mean change in CD4 count from baseline CD4 counts were 99 for NVP, 124 for IDV, and 118 for 3TC; confidence intervals were overlapping (see Table 6.7A in Statistical review).

Safety

No patients died while on study medications or within 30 days of stopping study medication.

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2. Indinavir 800 mg q8h + stavudine 40 mg bid (30 mg bid if body weight < 60 kg) + didanosine 400 mg qd (N=100)
3. Lamivudine 150 mg bid + stavudine 40 mg bid (30 mg bid if body weight < 60 kg) + didanosine 400 mg qd (N=109).

Outcome measures: The primary endpoint is the proportion of patients with HIV-1 RNA less than 500 copies/ml at 48 weeks.

Study Population: Two-hundred-ninety-eight antiretroviral naïve patients with asymptomatic HIV infection, HIV RNA \geq 500 copies/ml and CD4+ T-cell count \geq 200/ml were enrolled. Patients were excluded with the following laboratory values during screening: Hemoglobin less than 7 mmol/l (< 6.5 for women), absolute neutrophil count < 750/ml, thrombocyte count < 25,000/ml, ALT/AST \geq 5 X ULN, or serum creatinine > 1.5 x ULN. Demographic characteristics for the patients included 70% from Europe, 30% from North America. The median age for all patients was 35.5 years. Eighty percent were male; 92% were CDC stage A, 7% stage B, and 1% stage C. The median CD4 count was 406 cells/ μ l, median log₁₀ HIV-1 RNA 4.25, 12.8 % of subjects had baseline HIV-1 RNA > 100,000 copies/ml. Source: Table 11.2.1, Vol. 60, page 48.

Efficacy results

Table 12. Proportion of subjects HIV-RNA < 500 copies/ml at 48 weeks, intention-to-treat analysis

Treatment group	Proportion < 500 copies/ml at 48 weeks (%)	Confidence intervals, 95%
NVP-d4T-ddI	52/89 (58)	(48.2-68.7)
IDV-d4T-ddI	57/100 (57)	(47.3-66.7)
3TC-d4T-ddI	64/109 (59)	(49.5-68.0)

Source: Table 11.4.4, vol. 60, page 51

Mean CD4 counts increased for all three treatment groups during the study. There were no significant differences between treatment groups with respect to initial immunologic response or sustained response (Source: Volume 60, page 78). The mean change in CD4 count from baseline CD4 counts were 99 for NVP, 124 for IDV, and 118 for 3TC; confidence intervals were overlapping (see Table 6.7A in Statistical review).

Safety

No patients died while on study medications or within 30 days of stopping study medication.

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Table 13. Adverse events occurring in at least 20 patients in the study by treatment group

Adverse event	NVP-d4T-ddI (N=85) n (%)	IDV-d4T-ddI (N=94) n (%)	3TC-d4T-ddI (N=104) n (%)
Nausea, vomiting	26 (31)	38 (40)	28 (27)
Diarrhea, loose stool	22 (26%)	33 (35%)	20 (19%)
Peripheral neuropathy, paresthesias, transient numbness/tingling	14 (16)	11 (12)	18 (17)
Headache	15 (18)	15 (16)	12 (12)
Fatigue	10 (12)	10 (11)	12 (12)
Abdominal pain	8 (9)	11 (12)	10 (10)
URI, cough, cold, sinusitis	9 (11)	8 (9)	12 (12)
Rash or erythematous rash	16 (19)	7 (7)	3 (3)
Cough	10 (11)	5 (5)	7 (7)
Dry skin, ichthyosis, xeroderma, flaking skin	1 (1)	17 (18)	3 (3)
Nephrolithiasis	0	20 (21)	0

Source: Table 14.2.1-1, volume 59, pages 5-8 (revised February 23, 2001, pages 179-182).

Serious adverse events, see volume 59, page 12 (revised February 23, 2001, page 271): Note 4 SAEs due to rash in NVP group reported in narratives, only 3 listed in table (vol. 59, page 12).

M114901 (Barcelona) Cutaneous rash and fever at 12 days of therapy (see Vol. 61, page 374)

M13062 (Birmingham) rash described as severe at 24 days of therapy (61, 374).

M13350 (Paris) hospitalized for rash onset 4 days after starting NVP (61, 376).

M15885 (Vancouver) onset of fever, chills at day 9 of therapy evolved into SJS requiring hospitalization (61,376-7)

Hepatic events were rarely reported in the Atlantic study. Hepatic steatosis was listed for one patient in the NVP arm and one in the 3TC arm. Hepatomegaly was also listed for one patient in the NVP and one in the 3TC arm. Active symptomatic HCV infection was listed for two 3TC-treated patients, but none in the NVP or IDV arms See Table 14.2.1-1, Vol. 59, page 5; revised February 23, 2001, page 179).

Serious adverse events. Two serious adverse events were listed with serious HCV infection – both treated with 3TC arm (M15499 and M15681, narratives in vol. 61, page 379). One additional patient (M14894, narrative vol. 61, page 373) experienced severe

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hypertransaminasemia while assigned to IDV arm. No serious hepatic events were associated with NVP therapy.

Table 14. Laboratory abnormalities in at least 10 patients by treatment group

Laboratory abnormality	NVP-d4T-ddI (N=85) n (%)	IDV-d4T-ddI (N=94) n (%)	3TC-d4T-ddI (N=104) n (%)
Gamma-GT (elevated)	19 (22%)	3 (3%)	5 (5%)
CPK (elevated)	13 (15)	10 (11)	4 (4)
ALT (elevated)	5 (6)	4 (4)	10 (10)
AST (elevated)	5 (6)	3 (3)	8 (8)
Triglycerides (elevated)	3 (4)	2 (2)	8 (8)
Bilirubin (elevated)	0	10 (11)	2 (2)
Amylase (elevated)	3 (4)	2 (2)	5 (5)

Source: Table 14.2.1-1, volume 59, page 5.

Summary conclusions of the Atlantic Study (BI 1229)

The results of the Atlantic study support nevirapine in combination with other antiretroviral agents as safe and effective therapy in lowering viral load at 48 weeks. The study compared three treatment regimens, one including nevirapine, an NNRTI, one including indinavir, a protease inhibitor, and one including lamivudine, an NRTI, all in combination with didanosine + stavudine in antiretroviral naïve HIV-1 infected patients. The nevirapine dose was 200 mg once daily for two weeks, followed by 400 mg once daily – a dosage not currently approved in the labeling for nevirapine. All three of the treatment combinations were effective in the majority of patients as measured by virologic measures less than 500 copies/ml and increasing CD4 counts at 48 weeks. No statistically significant differences between treatment groups were observed.

Rash was more frequently and more severe for patients treated with nevirapine compared to those treated with the other regimens. No serious clinical hepatic events were reported with nevirapine.

The study results were not included in the final labeling because a non-approved dosage of nevirapine was employed and small numbers of patients to support equivalence. However, the study does support the use of nevirapine as a safe and effective agent for HIV-1 infection.

C. INCAS Study (BI 1046) – (starts with volume 69)

Title: A randomized, placebo-controlled, double-blinded multinational trial comparing the immunologic and virologic effects of nevirapine, didanosine, and zidovudine

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combinations for the treatment of antiretroviral naïve HIV-1 infected patients with 200-600 CD4+ T-cells and no AIDS defining disease. INCAS refers to the participant countries, Italy, the Netherlands, Canada, and Australia.

Objective: To compare the virologic and immunologic activity of nevirapine + zidovudine, of zidovudine + didanosine, and of nevirapine + zidovudine + didanosine. To assess the safety and tolerability of two and three drug combinations of nevirapine, zidovudine and didanosine.

Study Design: This was a phase 3 randomized, multicenter, placebo-controlled study conducted in Australia, Canada, Italy, and the Netherlands. The first patient was randomized on September 15, 1994 and the last patient, on May 10, 1995. The treatment arms were as follows:

1. Nevirapine 200 mg qd for 14 days, then nevirapine 200 mg bid + zidovudine 600 mg qd + didanosine 250 or 400 mg qd dependent on weight of subject (N=51)
2. Nevirapine 200 mg qd for 14 days, then nevirapine 200 mg bid + zidovudine 600 mg qd + didanosine placebo (N=47)
3. Nevirapine placebo + zidovudine 600 mg qd + didanosine 250 or 400 mg qd dependent on weight of subject (N=53)

Outcome measures: The primary endpoint compared the HIV-1 RNA log-transformed proportionate change from baseline. The change from baseline in mean HIV-1 RNA levels and CD4+ cell counts at the average of visit results at weeks 40, 44, 48, and 52 weeks were analyzed. The primary analysis, using the Ultra-Direct method of Amplicor, allowed quantification of plasma HIV-RNA down to a level of detection of 20 copies/ml.

“The protocol stated that the end-of-year average should be calculated by averaging results for Weeks 44, 48, and 52. However, the analysis also utilized data from 40 weeks. This was done to increase the numbers of evaluable patients and number of observations for each patient. The decision to include Week 40 data was made prior to the unblinding. For completeness, analyses restricted to Weeks 44-52 are presented in Appendix 15.9.11. (Quoted from Volume 70, page 65).

There were two amendments to the protocol. In March 1994, the rash management guidelines, concomitant medication section, time-points for interim analysis and the role of the Data Safety Monitoring Board were updated. In August 1994, the inclusion criteria for LFTs were changed to ≤ 3 times from ≤ 5 times the upper normal limit.

Study Population: One-hundred fifty-three patients were enrolled. Two patients did not receive study drug. Three additional patients (one NVP/ZDV, 2 ddI/ZDV patients) did not have evaluable post-treatment HIV RNA results and another patient (NVP/ZDV) did not have an evaluable baseline HIV-RNA.

The study was that of predominantly white males (approximately 95% white and 93% male). The mean age was approximately 37 years, median baseline CD4 counts

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approximately 373 cells/ml. The median baseline HIV RNA levels were 17,732 copies/ml for the NVP/ddI/ZDV group, 32,163 for ddI/ZDV, and 48,654 for NVP/ZDV. There were no significant differences between the three treatment groups.

Early discontinuations were seen in 14/51 (28%) of those treated with NVP/ddI/ZDV, 18/53 (34%) with ddI/ZDV, and 20/47 (43%) with NVP/ZDV.

Table 15. Efficacy results - Outcome of randomized treatment through 48 weeks

Outcome	NVP/ddI/ZDV	ZDV/ddI	NVP/ZDV
HIV-RNA < 400 copies/ml at 48 weeks	23 (45%)	10 (19%)	0 (0%)
Confirmed rebound	18 (35)	20 (38)	23 (49)
Never less than 400 copies/ml	6 (12)	20 (38)	20 (43)
CDC category C event	1 (2)	0	0
Lost to follow-up	3 (6)	1 (2)	3 (6)
No viral specimens	0	2 (4)	1 (2)
Total	51 (100)	53 (100)	47 (100)

Source: Table 5.3.1.1:7, volume 68, page 16 and text; modified and as reported in statistical review, Table 4.6B.

The average change of CD4 count from baseline to week 52 was 99 cells/ml for the NVP/ddI/ZDV arm, 66 cells/ml for the ddI/ZDV arm, and 35 cells/ml for the NVP/ZDV arm.

Safety

There were three deaths during the study – one from each treatment group (See volume 77).

Patient No. 3431 (NVP/ddI/ZDV) 47 year-old male in the Netherlands was diagnosed with non-Hodgkin's lymphoma on day 322, followed by episodes of pneumonia, severe radicular pain, paresis, and ptosis. Other complications included pneumonias, abdominal melanoma, and leukopenia. He stopped study drugs on day 389 and died by euthanasia on day 464.

Patient 3382 (ZDV/ddI) 35 year-old Canadian male experienced confusion, visual hallucinations, pneumonia and rash and went to the ER on day 9, from which the patient was admitted and study drugs were stopped. PML was ultimately diagnosed and he died on day 316.

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Patient 3373 (NVP/ZDV) 46 year-old Canadian male with a history of depression attempted suicide on day 21 and was hospitalized. He was discharged on antidepressant medication on day 34. He committed suicide on day 223.

Table 16. Adverse events regardless of causality

Adverse Event	NVP/ddI/ZDV (N=51)	ZDV/ddI (N=53)	NVP/ZDV (N=47)
Nausea	39 (76%)	35 (66%)	32 (68%)
Upper respiratory infection	25 (49)	23 (43)	24 (51)
Headache	19 (37)	23 (43)	22 (47)
Diarrhea	17 (33)	19 (36)	13 (28)
Fatigue	14 (27)	19 (36)	15 (32)
Vomiting	19 (37)	11 (21)	16 (34)
Pain	15 (29)	15 (28)	13 (28)
Rash	15 (29)	8 (15)	15 (32)
Abdominal pain	13 (25)	9 (17)	14 (30)
Insomnia	16 (31)	10 (19)	8 (17)
Abnormal LFTs	8 (16)	5 (9)	10 (21)

Rash included rash, erythematous rash and maculopapular rash.

Source: Table 10.2.3:1, Volume 70, page 92.

Table 17. Nevirapine-related adverse events

Adverse Event	NVP/ddI/ZDV (N=51)	ZDV/ddI (N=53)	NVP/ZDV (N=47)
Nausea	21 (41%)	16 (30%)	20 (43%)
Rash	12 (24)	3 (6)	10 (24)
Fatigue	8 (16)	12 (23)	9 (19)
Headache	6 (12)	6 (11)	11 (23)
Abnormal LFTs	5 (10)	2 (4)	8 (17)

Rash includes rash, erythematous rash, and maculopapular rash.

Source: Table 10.2.3:2, Volume 70, page 93

Summary conclusions of INCAS (BI 1046)

The results of INCAS support nevirapine in combination with other antiretroviral agents as safe and effective therapy in lowering viral load at 48 weeks. The study compared three treatment regimens, one three-drug arm including nevirapine, didanosine, and zidovudine and two-drug arms, didanosine/zidovudine and nevirapine/zidovudine, in antiretroviral-naïve HIV-1 infected patients. The nevirapine dose was 200 mg once daily for two weeks, followed by 200 mg twice daily thereafter. The virologic responder rates at 48 weeks were 45% for patients treated with NVP/ZDV/ddI, 19% for ZDV/ddI and 0% for NVP/ZDV.

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Rash was reported in about one-quarter of nevirapine-treated patients. Abnormal liver function test results were reported more frequently for nevirapine-treated patients compared to control patients.

4. Integrated Summary of Safety

In addition to the data submitted in the May 2001 NDA submission, we reviewed safety data in NDA 20-636, Supplement S-017, Amendment 2 submitted September 24, 2001, and IND 36,026, Serial Number 381 submitted September 25, 2001.

Several Periodic Safety Updates were submitted during the review cycle: NDA 20-933, P-012 on October 10, 2001; 20-636, P-018 on July 20, 2001 and 20-636, P-019 on October 19, 2001. None of the reports raised any additional issues regarding the current safety profile of nevirapine.

Hepatotoxicity

Clinical hepatic adverse events are referred to as hepatitis and related hepatic events and include hepatitis, cholestatic hepatitis, infectious hepatitis, hepatic failure. Clinical hepatitis also included patients with an increase in LFTs as described below plus concurrent clinical signs and symptoms compatible with emergent hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, acholic stools, liver tenderness or hepatomegaly. Increased LFTs were defined as an increase from baseline to the maximum value of either SGOT or SGPT to Grade 3 (5x ULN) or an increase to 2x baseline.

In Study BI 1090 clinical hepatic adverse events were more common in the nevirapine-treated arm, 38/1121 (3.4%) compared to the placebo arm 22/1128 (2.0%), and were more frequently attributed to antiretroviral treatment in the NVP arm. The cumulative probability of hepatitis or related events at 1 year was 3.4% for nevirapine versus 2.2% for placebo. The proportions of patients for whom the hepatic event led to temporary discontinuation of blinded medication was greater for NVP treatment, 15/1121 (1.3%) versus 2/1121 (0.2%). However, the proportion of patients for whom permanent discontinuation of blinded medication resulting from hepatic events was similar for NVP (0.9%) and placebo (0.8%), as were deaths due to hepatic events, 2 for NVP and 3 for placebo.

In the three additional safety studies, BI 1037, 1038 and 1046, hepatotoxic adverse events were more common in the nevirapine arm 15/253 (5.9%) compared to 1/203 (0.5%). The cumulative probability of hepatitis or related events at 1 year was 8.1% for nevirapine versus 3.0% for placebo. Three adverse hepatic events in the NVP arm led to permanent discontinuation. No deaths due to hepatic events were reported in these three studies.

Composite – In the four controlled studies, BI 1090, 1037, 1038, and 1046, hepatitis and related hepatic events were more common in the nevirapine-treated arm 53/1374 (3.9%) compared to the placebo arm 23/1331 (1.7%). Permanent discontinuation of blinded medication resulted from hepatic events in 18 patients treated with NVP versus 2 patients

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treated with placebo. Two deaths were attributed to drug-induced hepatotoxicity in the NVP arm, three in the placebo arm.

Among patients in BI 1090, who had hepatitis or hepatic events, the maximum liver function tests are shown in the following table.

Table 18. Liver function test results by treatment

	Nevirapine (n = 38 of 1121)	Placebo (n = 22 of 1128)
Maximum ALT or AST		
Grade 0 ($\leq 1.25 \times$ ULN)	2	0
Grade 1 ($> 1.25 \times$ ULN)	2	1
Grade 2 ($> 2.5 \times$ ULN)	4	7
Grade 3 ($> 5.0 \times$ ULN)	4	6
Grade 4 ($> 7.5 \times$ ULN)	26	8
Maximum bilirubin		
Grade 0 ($\leq 1.0 \times$ ULN)	18	10
Grade 1 ($> 1.0 \times$ ULN)	10	6
Grade 2 ($> 1.5 \times$ ULN)	1	2
Grade 3 ($> 2.5 \times$ ULN)	4	2
Grade 4 ($> 5.0 \times$ ULN)	5	2

Similar results are obtained for Combined trials 1037, 1038, and 1046. Among patients with hepatic events, monitoring ALT and AST appears to have more predictive value than serum bilirubin testing.

Table 19. Analysis of patients with Grade 3 or 4 AST/ALT elevations observed during blinded treatment in Trial 1090

Patients with Grade 3 or 4 transaminase elevations	Nevirapine (n=1121)	Placebo (n=1128)
Grade 3 ($> 5.0 \times$ ULN)	37 (3.3%)	48 (4.3%)
Grade 4 ($> 7.5 \times$ ULN)	53 (4.7%)	43 (3.8%)

One can conclude that 30 patients (or 33%) in Study 1090 developed clinical hepatic events out of the 90 patients reaching at least Grade 3 transaminase elevation for the nevirapine arm, 14/91 (15%) for placebo. For studies BI 1037, 1038 and 1046, 13/36 (36%) of those with at least Grade 3 transaminase elevation developed clinical hepatic events; 1/10 in the control groups.

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Table 20. The timing of onset of the 53 hepatic events in the NVP-treated arms of the four controlled clinical trials, BI 1090, 1037, 1038, and 1046

	Patients entering interval	No. of events within interval
Day 1-28	1374	12
Day 29-56	1282	7
Day 57-84	1228	6
Day 85-168	1168	10
Day 169-365	1042	10
Day 366-547	660	6
Day 548-730	309	2

Although 47% of the hepatic events occur in the first 12 weeks of therapy, the majority of hepatic events occurred at later time points. Continuous monitoring is recommended.

Baseline transaminase elevation as a risk factor for hepatic events.

Table 21. Hepatitis or related hepatic events stratified by baseline transaminases

Baseline AST/ALT	Trial 1090 NVP – events/total (%), [1-year cumulative probability]	Other Trials* NVP – events/total (%), [1-year cumulative probability]	Trial 1090 Placebo – events/total (%), [1-year cumulative probability]	Other Trials* Placebo – events/total (%), [1-year cumulative probability]
Grade 0 ($\leq 1.25 \times \text{ULN}$)	21/745 (2.8%) [2.7%]	8/199 (4%) [7.2%]	10/748 (1.3%) [1.3%]	1/155 (0.6%) [4.2%]
\geq Grade 1 ($> 1.25 \times \text{ULN}$)	17/358 (4.7%) [4.8%]	7/53 (13.2%) [12.2%]	12/363 (3.3%) [4.0%]	0/48

* Trials BI 1037, 1038 and 1046.

Source: Table 5.5.1.3:5, volume 4, page 89

Table 22. Hepatic events stratified by baseline transaminases

Baseline AST/ALT	Trial 1090 NVP – events/total (%), [6-month cumulative probability]	Other Trials* NVP – events/total (%), [6-month cumulative probability]	Trial 1090 Placebo – events/total (%), [6-month year cumulative probability]	Other Trials* Placebo – events/total (%), [6-month cumulative probability]
Grade 0 ($\leq 1.25 \times \text{ULN}$)	22/751 (2.9%) [1.9%]	8/200 (4%) [3.3%]	10/755 (1.3%) [0.6%]	1/156 (0.6%) [0%]
Grade 1 ($> 1.25 \times \text{ULN}$)	11/267 (4.1%) [2.5%]	3/35 (8.6%) [6.0%]	6/272 (2.2%) [1.6%]	0/35
Grade 2	4/72 (5.6%)	4/15 (26.7%)	4/74 (5.4%)	0/10

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(> 2.5 x ULN)	[5.9%]	[27.3%]	[4.7%]	
Grade 3	1/13 (7.7%)	0/2	2/10 (20.0%)	0/2
(> 5x ULN)	[0.0%]		[25.0%]	

Source: Amendment to supplement, NDA 20-636, September 24, 2001, page 23.

Trial 1090 provided a unique opportunity to examine co-infection with HBV and/or HCV as a risk factor for hepatic events because the serologic status of all patients was determined at baseline (not documented for all patients in Studies BI 1037, 1038 and 1046). The risk of adverse hepatic events was 4-6 fold higher for patients with pre-existing HBV or HCV infection independent of treatment regimen.

Table 23. Number of hepatitis or related hepatic events in trial 1090, stratified by baseline HBV or HCV serologic status

HBV or HCV serology at baseline	NVP - Number events/total (%), [one-year cumulative probability]	Placebo - Number events/total (%), [one-year cumulative probability]
Negative for both HBV/HCV	17/814 (2.1%) [1.8%]	6/795 (0.8%) [0.9%]
Positive for HBV +/-or HCV	21/294 (7.1%) [7.8%]	16/326 (4.9%) [5.2%]

Table 24. Hepatitis or related hepatic events in trial 1090 among subjects HBV and/or HCV positive at baseline stratified by baseline transaminase levels

Baseline LFT relative to ULN	Nevirapine treatment* [6-month cumulative probability]	Placebo treatment* [6-month cumulative probability]
≤ 1.25	12 / 143 (8.4%) [6.2%]	8 / 168 (4.8%) [1.9%]
> 1.25 - 2.5	6 / 106 (5.7%) [4.3%]	5 / 112 (4.5%) [2.8%]
> 2.5-5.0	3 / 39 (7.7%) [8.0%]	2 / 35 (5.7%) [3.5%]
> 5.0	0 / 3 (0.0%) [0.0%]	1 / 6 (16.7%) [16.7%]
Total	21 / 291 (7.2%)	16 / 321 (5.0%)

* Baseline data missing for some patients

Source: Table 4.3.2.2: Page 26 of IND 36,026, SN 381, submitted September 25, 2001

Table 25. Hepatitis or related hepatic events in trial 1090, HBV and HCV negative at baseline stratified by baseline transaminase levels

Baseline LFT relative to ULN	Nevirapine treatment*	Placebo treatment*
≤ 1.25	10/601 (1.7%) [0.9%]	2/582 (0.3%) [0.2%]
> 1.25 - 2.5	5/156 (3.2%) [1.3%]	1/158 (0.6%) [0.7%]
> 2.5-5.0	1/32 (3.1%) [3.5%]	2/39 (5.1%) [5.6%]
> 5.0	1/10 (10%) [0%]	1/4 (25%) [33.3%]
Total	17/799 (2.1%)	6/783 (0.7%)

* Baseline data missing for some patients

Source: Table 4.3.2.2: Page 26 of supplement to NDA 20-636, submitted September 24, 2001

Table 26. The increased rate of clinical hepatic events in the combined studies BI 1037, 1038, and 1046 may be related to nevirapine and higher baseline CD4+ cell counts

Baseline CD4+ count	NVP - Number events/total (%), [one-year cumulative probability]	Placebo - Number events/total (%), [one-year cumulative probability]
< 350 cells/ml	4/114 (3.5%) [2.9%]	0/89 (0%)
≥ 350 cell/ml	11/139 (7.9%) [13.1%]	1/114 (0.9%) [5.0%]

Source: Table 5.5.1.3:2, volume 4, page 85.

In study BI 1090 the risk of hepatitis or related events were estimated to increase by 36% for each 50-cell/ml increase of maximum CD4+ count during treatment. One might hypothesize that the lower rates of hepatic adverse events in BI 1090 result from a study population with lower CD4 counts on entry than those patients in BI 1037, 1038 and 1046. It is possible that nevirapine-induced hepatotoxicity is through an immunologic mechanism, and such an hypothesis might help explain the anecdotes of severe hepatotoxicity in post-exposure prophylaxis patients, patients with higher CD4 counts when nevirapine was initiated (See MMWR, January 5, 2001).

Table 27. Hepatitis and related hepatic events, stratified by demographics and baseline disease characteristics

		Trial 1090		Trials 1037, 1038, 1046	
		NVP (n=1121)	Placebo (n=1128)	NVP (n=253)	Placebo (n=203)
Sex	Female	7/242 (2.9%)	1/226 (0.4%)	1/25 (4%)	0/11 (0%)
	Male	31/879 (3.5%)	21/902 (2.3%)	14/228 (6.1%)	1/192 (0.5%)
Race	Black	12/276 (4.4%)	2/263 (0.8%)	2/29 (6.9%)	0/18 (0%)
	White	26/778 (3.4%)	17/792 (2.2%)	11/199 (5.5%)	1/168 (0.6%)
	Other	0/67 (0%)	3/73 (4.1%)	2/25 (8.0%)	0/17 (0.0%)
Alcoholism	No	2.8%	1.8%	6.2%	0.6%
	Yes	7.6%	3.4%	4.9%	0%
IV drug use	Never	2.9%	1.3%	6.3%	0.6%
	Stopped	5.4%	4.8%	4.4%	0%

Source: Table 4.2.2:1, Page 13 of IND 36,026, SN 381, submitted September 25, 2001 and Table 5.5.1.3:7 of NDA Volume 4, page 92.

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Table 26. The increased rate of clinical hepatic events in the combined studies BI 1037, 1038, and 1046 may be related to nevirapine and higher baseline CD4+ cell counts

Baseline CD4+ count	NVP - Number events/total (%), [one-year cumulative probability]	Placebo - Number events/total (%), [one-year cumulative probability]
< 350 cells/ml	4/114 (3.5%) [2.9%]	0/89 (0%)
≥ 350 cell/ml	11/139 (7.9%) [13.1%]	1/114 (0.9%) [5.0%]

Source: Table 5.5.1.3:2, volume 4, page 85.

In study BI 1090 the risk of hepatitis or related events were estimated to increase by 36% for each 50-cell/ml increase of maximum CD4+ count during treatment. One might hypothesize that the lower rates of hepatic adverse events in BI 1090 result from a study population with lower CD4 counts on entry than those patients in BI 1037, 1038 and 1046. It is possible that nevirapine-induced hepatotoxicity is through an immunologic mechanism, and such an hypothesis might help explain the anecdotes of severe hepatotoxicity in post-exposure prophylaxis patients, patients with higher CD4 counts when nevirapine was initiated (See MMWR, January 5, 2001).

Table 27. Hepatitis and related hepatic events, stratified by demographics and baseline disease characteristics

		Trial 1090		Trials 1037, 1038, 1046	
		NVP (n=1121)	Placebo (n=1128)	NVP (n=253)	Placebo (n=203)
Sex	Female	7/242 (2.9%)	1/226 (0.4%)	1/25 (4%)	0/11 (0%)
	Male	31/879 (3.5%)	21/902 (2.3%)	14/228 (6.1%)	1/192 (0.5%)
Race	Black	12/276 (4.4%)	2/263 (0.8%)	2/29 (6.9%)	0/18 (0%)
	White	26/778 (3.4%)	17/792 (2.2%)	11/199 (5.5%)	1/168 (0.6%)
	Other	0/67 (0%)	3/73 (4.1%)	2/25 (8.0%)	0/17 (0.0%)
Alcoholism	No	2.8%	1.8%	6.2%	0.6%
	Yes	7.6%	3.4%	4.9%	0%
IV drug use	Never	2.9%	1.3%	6.3%	0.6%
	Stopped	5.4%	4.8%	4.4%	0%

Source: Table 4.2.2:1, Page 13 of IND 36,026, SN 381, submitted September 25, 2001 and Table 5.5.1.3:7 of NDA Volume 4, page 92.

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Skin Rash

The databases for Trials 1090, 1037, 1038, and 1046 were reviewed for patients with rash including those patients with any skin manifestation or allergic reaction that represent a rash or a part of a rash/symptom complex. Events that were clearly identified as viral exanthemas, scabies, contact dermatitis, folliculitis, or isolated pruritus were excluded from these analyses. Rashes are graded as follows:

Grade 1 – erythema, pruritis

Grade 2 – diffuse, no constitutional findings, or urticarial rash

Grade 3 – rash with constitutional findings

Grade 4 – rash with skin detachment covering >10%

In trial 1090, rashes were identified in 253/1121 (22.6%) patients in the nevirapine group and 158/1128 (14%) in the placebo group.

Table 28. Summary of rash observed during blinded treatment in Trial 1090

	NVP – (N=1,121 patients)	Placebo – (N=1,128 patients)
Patients with rash	253 (22.6%)	158 (14.0%)
Intensity		
Mild	156 (61.7%)	113 (71.5%)
Moderate	79 (31.2%)	44 (27.8%)
Severe	18 (7.1%)	1 (0.6%)
Functional groups		
Grade 1	96 (37.9%)	78 (49.4%)
Grade 2	127 (50.2%)	70 (44.3%)
Grade 3	30 (11.9%)	10 (6.3%)
Grade 4	0	0
Patients who permanently discontinued blinded medication with rash	51 (4.5% of patients) (20.2% of rashes)	15 (1.3% of patients) (9.5% of rashes)
Timing of initial rash		
Day 1-14	89 (35.2%)	40 (25.3%)
Day 15-28	46 (18.2%)	14 (8.9%)
Day 29-42	17 (6.7%)	12 (7.6%)
Day 43-84	31 (12.3%)	30 (19.0%)
Day 85-168	30 (11.9%)	26 (16.5%)
Day 169-365	28 (9.9%)	24 (15.2%)
Missing data	12 (4.7%)	12 (7.6%)
Timing of Grade 3 rashes		
Day 1-14	16 (53.3%)	0
Day 15-28	4 (13.3%)	0
Day 29-42	3 (10.0%)	1 (10%)
Day 43-365	6 (20.0%)	8 (80%)
Missing data	1 (3.3%)	1 (10%)

Source: Table 5.5.2.1:1, Vol. 4, page 96.

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One patient in BI 1090 (No. 7841) developed Stevens-Johnson Syndrome (SJS) while taking nevirapine. Another patient (No. 7284) from the placebo group developed SJS after completing therapy; the patient never took nevirapine. SJS was attributed to the use of trimethoprim/sulfa.

In Trials BI 1037, 1038, 1046, rashes were identified in 63/253 (24.9%) patients in the nevirapine group and 28/203 (13.8%) in the placebo group.

Table 29. Summary of rash observed during blinded treatment in Trials BI 1037, 1038, and 1046

	NVP – (N=253 patients)	Placebo – (N=203 patients)
Patients with rash	63 (24.9%)	28 (13.8%)
Intensity		
Mild	43 (68.3%)	21 (75.0%)
Moderate	15 (23.8%)	4 (14.3%)
Severe	5 (7.9%)	3 (10.7%)
Functional groups		
Grade 1	21 (33.3%)	11 (39.3%)
Grade 2	34 (54.0%)	15 (53.6%)
Grade 3	8 (12.7%)	2 (7.2%)
Grade 4	0	0
Patients who permanently discontinued blinded medication with rash	8 (3.2% of patients) (12.7% of rashes)	1 (0.5% of patients) (3.6% of rashes)
Timing of initial rash		
Day 1-14	33 (52.4%)	6 (21.4%)
Day 15-28	14 (22.2%)	2 (7.1%)
Day 29-42	1 (1.6%)	4 (14.3%)
Day 43-84	4 (6.3%)	2 (7.1%)
Day 85-168	9 (14.3%)	1 (3.6%)
Day 169-365	1 (1.6%)	10 (35.7%)
Missing data	1 (1.6%)	1 (3.6%)
Timing of Grade 3 rashes		
Day 1-14	4 (50%)	0
Day 15-28	4 (50%)	0
Day 29-42	0	1 (50%)
Day 43-365	0	1 (50%)
Missing data	0	0

Source: Table 5.5.2.2:1, Vol. 4, page 100.

Three-quarters of the rashes occurred in the first 12 weeks of nevirapine therapy. Women were somewhat more prone to rash than men. In the controlled trials, 73/267 (27.3%) women developed rash compared to 240/1107 (21.7%) of men. The risk of Grade 3 rash was not elevated among women compare to men. The following table

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shows the proportion of patients in the controlled studies with all rash or grade 3 rash, by gender.

Table 30. Rash by gender and study treatment.

	Trial 1090 NVP	Trials 1037, 1038, 1046 – NVP	Trial 1090 – Placebo	Trials 1037, 1038, 1046 – Placebo
All rash				
Females	68/242 (28.1%)	5/25 (20.0%)	37/226 (16.4%)	1/11 (9.1%)
Males	185/879 (21.0%)	55/228 (25.4%)	121/902 (13.4%)	27/192 (14.1%)
Grade 3 rash				
Females	6/242 (2.5%)	1/25 (4.0%)	2/226 (0.9%)	0/11
Males	24/879 (2.7%)	7/228 (3.1%)	8/902 (0.9%)	2/192 (1.0%)

Source: Table 5.5.2.3:2, volume 4, page 103

Table 31. Proportion of patients with rash or grade 3 rash, by CD4 cell count at baseline, Trials 1090, 1037, 1038, and 1046

	NVP [Risk Ratio]	Placebo
All rash		
CD4 < 100 cells/ml	155/603 (25.7%) [1.61]	92/575 (16.0%)
CD4 101-200 cells/ml	66/384 (17.2%) [1.38]	51/409 (12.5%)
CD4 201-299 cells/ml	50/207 (24.2%) [1.86]	25/93 (13.0%)
CD3 300-400 cells/ml	20/77 (26.0%) [4.26]	4/66 (6.1%)
CD4 > 400 cells/ml	24/95 (25.3%) [2.11]	9/75 (12.0%)
Grade 3 rash		
CD4 < 100 cells/ml	17/603 (2.8%) [5.60]	3/575 (0.5%)
CD4 101-200 cells/ml	7/384 (1.8%) [1.06]	7/409 (1.7%)
CD4 201-299 cells/ml	9/207 (4.3%) [8.60]	1/191 (0.5%)
CD3 300-400 cells/ml	3/77 (3.9%) [--]	0/66
CD4 > 400 cells/ml	2/95 (2.1%) [1.6]	1/75 (1.3%)

Risk Ratio = Crude relative rate – NVP/placebo

Source: Tables 5.5.2.3:3 and 5.5.2.3:4, volume 4, pages 103 and 104.

6. Reviewer's assessment of efficacy and safety of nevirapine.

In support of the safety and efficacy of nevirapine in combination with other antiretroviral agents in adults, the applicant has submitted the results of one large, principal trial of more than 48 weeks duration and two smaller controlled trials of 48 weeks duration. The sponsor has also provided safety experience from a total of five controlled trials, and discussions of safety data from additional clinical trials and post-marketing experience.

The fact that the large principal study, BI 1090, demonstrated superiority in a controlled trial in advanced HIV-1 infected patients, and the supportive studies demonstrated efficacy in different patient populations, are convincing evidence of long term efficacy of nevirapine. Although the principal study was not powered to compare groups by race and gender, results favoring nevirapine over placebo were maintained for males and females and for two racial groups, i.e., whites and Blacks. There were no studies involving pediatric patients included in this NDA package.

There are several safety concerns when using nevirapine in combination with other antiretroviral agents in the treatment of HIV-1 infection. Based on the safety results of the controlled clinical trials, BI 1090, 1037, 1038, and 1046, hepatotoxicity and skin rash are the most important adverse events reported with nevirapine use.

Serious hepatic adverse events, including hepatic failure, hepatitis, cholestatic hepatitis, and infectious hepatitis, were more common in nevirapine-treated patients (53/1374 or 3.9%) compared to placebo (23/1331 or 1.7%). Serious hepatic adverse events also included patients presenting with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. These events have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia. Rash and fever accompanied some of these hepatic events. Hepatitis and related hepatic events continue to occur throughout nevirapine treatment. The likelihood of hepatitis or related clinical hepatic events during each week of treatment is highest during the first 2-4 months; 47% of the nevirapine-associated hepatic events occurred in the first 12 weeks of therapy, 85% during the first year of therapy. Patients with signs or symptoms of hepatitis must immediately seek medical evaluation, have liver function tests performed, and be advised to discontinue nevirapine as soon as possible.

Three factors were associated with greater risk of hepatic adverse events in the controlled clinical trials. Prior HBV or HCV infection quadruples the risk of hepatitis or related hepatic events for both nevirapine and control patients. Elevated baseline transaminases (> 1.25 times upper limit of normal for ALT and/or AST) doubles the risk for both nevirapine and control patients. Patients with higher baseline CD4+ cells counts (> 350

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CD4+ cells/ml) and treated with nevirapine may be at greater risk for elevated transaminases, hepatitis and related hepatic events.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis, an unapproved use.

Intensive clinical and laboratory monitoring is essential at baseline and during therapy with nevirapine. Liver function tests should be performed if a patient experiences signs or symptoms suggestive of hepatitis and/or a hypersensitivity reaction. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible.

If clinical hepatitis occurs, nevirapine should be permanently discontinued and not restarted after recovery.

In the clinical trials, rash was the most common adverse event reported; 23% (316/1374) of patients treated with nevirapine and 14% (186/1331) control patients developed rash. The nevirapine associated rash occurred most frequently [63% (200/316)] in the first six weeks of therapy, but also occurred at later times. Severe rashes with blistering, desquamation, or ulceration were reported in 23/316 (7.2%) of nevirapine-treated patients with rash compared to 4/186 (2.2%) of control patients with rash; one nevirapine-treated patient developed Stevens-Johnson Syndrome as did one placebo-treated patient - attributed to trimethoprim-sulfa. Severe rash or rash accompanied by constitutional findings, such as fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, and renal dysfunction was reported in the clinical trials. Thirty-eight nevirapine treated patients developed rash with constitutional findings (38/1374 - 2.8%) compared to 12/1331 (1.0%) of control patients. Over 80% of the nevirapine-associated rashes with constitutional findings occurred in the first six weeks of therapy.

Women were somewhat more prone to rash compared to men. In the controlled trials, 73/267 (27%) of women treated with nevirapine developed rash compared to 240/1107 (22%) of men. The risk for Grade 3 rash (rash with constitutional findings) was not elevated among women compared to men.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (rash with constitutional findings) must discontinue nevirapine as soon as possible. Nevirapine should not be restarted following severe skin or hypersensitivity reactions. In addition, the 14-day lead-in period with nevirapine 200-mg daily dosing must be strictly followed. If rash of any severity is observed during the 14-day lead-in period, dose escalation should not occur until the rash is resolved. Patients should be monitored closely if isolated rash of any severity occurs.

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In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine-associated rash is not recommended.

Labeling discussions were focused on:

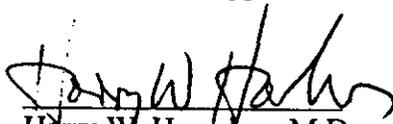
- Presentation of efficacy data from the principal study, BI 1090, presented as proportions of patients with HIV-RNA below assay limit of 50 copies/ml. and calculated using Kaplan-Meier estimates.
- Inclusion of data from the supportive study, INCAS, and the exclusion of the second supportive study, Atlantic, because of the use of a non-approved dosage of nevirapine.
- Provision of updated safety information regarding hepatotoxicity and rash in the Warnings and Precautions sections.
- Presentation of limited amount of available resistance data with some interpretation of results.

The following phase 4 commitments are proposed:

1. Submit the results of the 2NN study.
2. Evaluate multiple dose pharmacokinetics of nevirapine in subjects with hepatic impairment to allow the determination of dosing recommendations.
3. Determine the genotypes and phenotypes of multiple nevirapine resistant HIV-1 isolates from patients receiving nevirapine in combination with other antiretroviral agents. Please provide data on the correlation of nevirapine plasma concentrations and plasma viral load with emergence of nevirapine resistance mutations.
4. Review additional clinical trial data from ongoing and completed studies and evaluate the association between potential risk factors, including immunologic parameters (i.e., CD4 counts), race, gender, and development of hepatic adverse events.

7. Recommendations for regulatory action

This supplement supporting traditional approval of nevirapine should be approved. The applicant has fulfilled their accelerated approval phase 4 commitments. The final label is provided in an appendix.


Harry W. Haverkos, M.D.
Medical Officer, DAVDP

Concurrence:
HFD-530/DivDir/Birnkrant
HFD-530/TL/Kukich

Appears This Way
On Original

Group Leader's Memorandum

NDA: 20-636/017 and 20-933/007

Drug and Indication: Viramune® (nevirapine) tablets and oral solution for the treatment of HIV-1 infection in combination with other antiretroviral agents

Dose: 200 mg once daily for the first two weeks of treatment and then 200 mg twice daily

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Submission received: May 31, 2001

Date of MO review: March 22, 2002

Date of Memorandum: March 25, 2002

Boehringer Ingelheim Pharmaceuticals has requested traditional approval for Viramune® (nevirapine) tablets and oral solution, a non-nucleoside reverse transcriptase inhibitor, for the treatment of HIV-1 infection when used in combination with other antiretroviral agents. This indication is based on treatment-induced changes in plasma HIV RNA levels in controlled studies of at least 48 weeks duration. Sustained suppression in plasma HIV-1 RNA levels has been accepted as a surrogate endpoint that is reasonably likely to predict clinical benefit. The original New Drug Application for Viramune was approved on June 21, 1996 under accelerated approval regulations, 21 CFR 314 subpart H. An initial supplemental NDA that was intended to support the traditional approval was submitted in December 1997. However, it was withdrawn in June 1998 after a question was raised as to whether the submitted data would provide sufficient evidence of nevirapine treatment benefit.

In this supplemental NDA that is intended to fulfill the post-marketing commitments of accelerated approval, the applicant submitted the results of three controlled clinical trials 1100.1090, 1100.1229 (Atlantic) and 1100.1046 (INCAS). Together, these three studies randomized 2,605 patients. The data from the Trial 1100.1090, a 48-week controlled clinical trial in 2,249 HIV-infected patients provide principal support for traditional approval and provide evidence of treatment benefit for HIV-1 infected patients. Data from two smaller clinical trials serve as a supporting evidence of nevirapine safety and efficacy. In addition to these trials, the applicant has initiated 48-week, randomized, open-label, three-arm study to evaluate antiviral efficacy of nevirapine, efavirenz, and nevirapine/efavirenz in combination with d4T and lamivudine. This study was designed and powered to demonstrate non-inferiority of nevirapine twice-daily treatment compared to efavirenz.

Initiated in December 1995, the principal trial (1100.1090) was originally designed as clinical endpoint trial, however, with the introduction of HAART it became apparent that the study was not adequately powered to detect differences in clinical AIDS progression or death and on the recommendation of a Data Safety Monitoring Board the trial was stopped. After discussions with the Division and prior to unblinding of the data, the primary efficacy endpoint was changed to proportion of patients with virologic failure. This was the largest trial that enrolled 2,256 NNRTI-naïve patients with CD4 cell count <200 at screening. A median baseline CD4 cell count was 96 cells/mm³ and a baseline HIV RNA was 4.58 log₁₀ copies/mL (38,291 copies/mL). Prior to entering the trial, 45% of patients had previously experienced AIDS-defining clinical event. Patients were randomized to receive nevirapine/lamivudine or placebo/lamivudine on a background antiretroviral therapy.

The primary efficacy analysis was the proportion of patients with HIV RNA below the assay limit of quantification at week 48. Plasma HIV-1 RNA levels were measured using the unapproved Roche Amplicor UltraSensitive assay (ver. 1.5) with the limit of quantification (LOQ) of 50 copies/mL.

Other efficacy analysis presented in the nevirapine package insert was a time to virologic failure (TTF). In this analysis, patients who never achieved viral load below the limit of quantification of the assay were considered to have TTF of zero days. For patients who achieved viral load below the assay limit, TTF was measured from the onset of treatment to the first of a confirmed HIV RNA above the assay limit, an AIDS-defining event, death, change of study treatment for any reason or loss to follow up. Reduction in viral load below the assay limit and increase in CD4 cell counts was demonstrated in both, treatment-naïve and NRTI-experienced patients who received nevirapine. The efficacy of nevirapine was demonstrated in the TTF analysis. At each time point through 96 weeks for the nevirapine and the control arm, a higher fraction of patients treated with nevirapine compared to control had not reached the treatment failure endpoint.

The initial analysis of time to first AIDS-defining CDC event or deaths was suggestive of a small difference between nevirapine and placebo arms :

However, when as part of a sensitivity analysis CDC events and changes from assigned therapy were counted as failures in a Kaplan-Meier estimates by day 700, 26% of patients neither progressed or changed therapy in the nevirapine group compared to 13% in the placebo group.

The two smaller supportive trials also provided evidence of nevirapine efficacy. Safety information regarding nevirapine was based on four placebo-controlled trials (1100.1090, 1100.1046, 1100.1037 and 1100.1038), executive summaries of other clinical trials when nevirapine was a part of a treatment regimen, and the worldwide postmarketing surveillance safety database. Since 1996, it was estimated that has been approximately 260,000 person-years of nevirapine experience.

In four placebo-controlled clinical trials (nevirapine-placebo added to different treatment regimens), 1,374 patients received 200 mg twice daily, a marketed dose of nevirapine. The mean duration of exposure to nevirapine was 354 days and treatment exposure ranged from one to 781 days. The adverse events of primary concern were rash and hepatotoxicity. The incidence of rash in the nevirapine treated patients was 25.5% compared with 15% in the placebo group. Rash grade 3 or grade 4 that included erythema multiforme and Stevens-Johnson syndrome was reported in 2% of patients. The incidence of hepatic events (infectious hepatitis, cholestatic hepatitis and hepatic failure) was 3.2 and 1.3 in the nevirapine and placebo arm, respectively.

The one-year cumulative risk of hepatitis (infectious hepatitis, cholestatic hepatitis and hepatic failure) was 3.4 % for the nevirapine treated patients and 2.2 % for the placebo treated patients in study 1090 and 8% and 3%, respectively, in other three trials.

In the safety analysis by gender, the incidence of rash, nausea, and vomiting was higher in the females in the nevirapine group 31%, 19.5%, and 14.6 % than in the placebo group 15%, 12%, and 8.4%, respectively. The incidence of rash, nausea, and vomiting for male patients was 24%, 21%, and 11.5% in the nevirapine group and 16%, 20%, and 9% in the placebo group, respectively. The incidence of hepatic events for females in the nevirapine group was 2.3% and for females in the placebo group was 0.4%, however, for males was 3.4% and 1.5%, respectively.

There were 53 deaths among nevirapine treated patients. A majority of deaths were related to HIV-infection. Serious adverse events with the notably higher incidence rate in the nevirapine group were hepatitis, rash, and abnormal LFT's when compared with the placebo group. Adverse events leading to nevirapine discontinuation were rash, abnormal LFT's, fever, vomiting, abdominal pain, and hepatitis.

The following risk factors for hepatic events were identified during the review of the clinical trials data: pre-existing transaminase elevations, history of hepatitis B or C infection, higher baseline CD4 cell count. It appears that female patients may be at a greater risk for nevirapine-associated hepatic events and rash.

Detailed discussion of nevirapine safety and efficacy is provided in the medical and statistical review of this supplemental application. I am in agreement with the conclusions of the primary reviewers that this supplemental application should be approved. The efficacy of nevirapine in combination with other antiretroviral agents for the treatment of HIV-1 infection was demonstrated in studies longer than 48 weeks duration, which included treatment naïve and NRTI-experienced patients. The available safety information does not alter the overall understanding of the nevirapine safety profile.

Labeling discussions were focused on:

- a. Provision of balanced information in the Warning Section of the package insert about serious hepatic adverse events and clarifying that these events were reported

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most frequently during the first 12-16 weeks of treatment, however, the risk for these events continues past this period. Patients should be monitored intensively not only during the first 12-16 weeks of therapy but during entire treatment period. Providing information about risk factors associated with nevirapine-associated rash and hepatic events.

- b. Description of skin rash in the Adverse Reactions Section of the labeling.
- c. Presentation of the efficacy data as Kaplan-Meier estimates.

I am in agreement with the requested Phase IV commitments included in the approval letter for nevirapine and the applicant will commit to the following:

1. BIPI will work closely with IATEC, the IND holder for the 2NN study, to provide the results of the study to FDA in the fourth quarter of 2003.
2. BIPI will perform analyses to evaluate and attempt to determine appropriate dosing recommendations in patients with hepatic impairment by the second quarter of 2004.
3. BIPI commits to examine the genotypes and phenotypes of multiple nevirapine resistant HIV-1 isolates from patients receiving nevirapine in combination with other antiretroviral agents, and to provide data on the correlation of nevirapine plasma concentrations and plasma viral load response with the emergence of nevirapine resistance mutations in the 2NN study, in the fourth quarter of 2003.
4. BIPI commits to provide analyses of additional clinical trial data and evaluate the association between potential risk factors, including immunologic parameters (i.e. CD4 counts), race, gender, and development of hepatic adverse events, in the third quarter of 2002.


Stanka Kukich, M.D.
Medical Team Leader, HFD-530

cc:
NDA 20-636
HFD-530/DBirnkrant/HHaverkos/SKukich

/s/

Sean Belouin

1/19/01 03:37:58 PM

CSO

Hard copy signed-off by Kellie Reynolds-1/19/2001 and Jeff Murray-1/19
/2001