

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-933

MEDICAL REVIEW(S)

Medical Officer Review
of
, NDA 20-636, VIRAMUNER[®] Tablet
— and
NDA 20-933, VIRAMUNER[®] Suspension

Pediatric Supplement

Date submitted: 03/13/98
Date assigned: 03/13/98
Date reassigned: 06/18/98
Date completed: 08/28/98

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
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Drug: Trade Name: VIRAMUNER[®]
Generic Name: Nevirapine
Class: Non-nucleoside analog reverse transcriptase inhibitor

Dosage Form: Tablets (200 mg)
Oral suspension (50 mg/5 ml)

Approved Indication: In combination with nucleoside analogues for the treatment of HIV-1 infected adults who have experienced clinical and/or immunologic deterioration.

Pursued Indication: To expand the above indication to include children

Therapeutic Potential: Type P

Materials Received:

IND/NDA	Submission Date	Content	No. of Volumes
NDA 20-636	03/13/98	Pediatric supplement, Bioavailability/bioequivalence studies of the suspension and tablet dosage forms.	23
NDA 20-933	04/17/98	CMC of suspension	8
NDA 20-636 (requested by FDA)	07/16/98	Reports of singledose studies	1

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1. Introduction

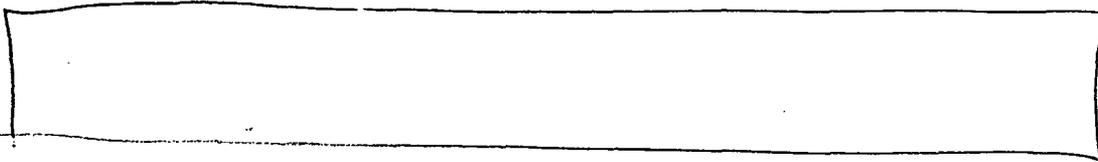
Nevirapine (NVP) is a dipyridodiazepinone derivative and is the first non-nucleoside reverse transcriptase inhibitor (NNRTI) to have been approved by the FDA. The marketing approval for the use of NVP in combination with nucleoside analogs in HIV-1 infected adults was granted in 1996 under the status of accelerated approval. In December of 1997, the applicant submitted an efficacy supplement (SEI 008) in an effort to obtain traditional approval for NVP. Based on a clinical/statistical joint review of this supplement, SEI 008 was recommended not approvable due to inadequate information on clinical endpoints presented in the trials. (For details, please refer to Dr. John Martin's review of 06/22/98.)

In order to pursue the marketing approval of NVP for the same indication in children, the applicant submitted these two NDAs (NDA 20-636 and NDA 20-933) providing pediatric clinical and pharmacokinetic data of NVP as tablets and suspension formulations.

The focus of this review is primarily on the applicant's safety analyses of NVP in pediatric patients. For a discussion of chemistry and manufacturing control of NVP suspension, please refer to Dr. George Lunn's review. For the discussion of pk profile of NVP in children, bioequivalence data of NVP suspension and the rationale for a dose recommendation in children, please refer to Dr. Vanitha Sekar's review.

2. Background

The development of the suspension formulation of NVP for pediatric use was initiated at the early stage of clinical trials of the tablet dosage form in adults. The study design of phase 1 pediatric trials of NVP had undergone many revisions which were primarily prompted by the emergence of reduced NVP sensitivity in isolates from treated adult patients. As a result, use of NVP in pediatric trials had evolved from monotherapy to double therapy with zidovudine (ZDV) and finally triple therapy with ZDV and didanosine (ddI).



requested.

3. Clinical Studies

The following table provides a complete list of all clinical studies in support of the pediatric supplement. Studies that appear in **bold-face** type are the sources for the entire safety database, thus they are the subjects of this review.

Study Number	Protocol Design	Treatment Regimen(s)	Study Duration (initiation to completion date)	No. of patients enrolled; nucleosides status
Completed Studies				
1100.882 (ACTG 180)	Open-label, pk, safety, efficacy	NVP, NVP/ZDV, or NPV/ZDV/ddI	6 mos. 10/91 - 6/96	37 children; naive and experienced
1100.853 (ACTG 165)	Open-label, single dose pk	NVP	6/91 - 10/91	9 HIV-infected children
1100.896	Open-label, 4-way crossover, relative bioavailability of pediatric suspension	NVP	10/91 - 1/92	15 adult volunteers
1100.1032 (ACTG 245)	Randomized, double-blind, placebo-controlled	NVP/ZDV/ddI vs. ZDV/ddI vs. NVP/ddI	48 week + ext. (8/94 - 7/97)	431 children (305 NVP treated)/experienced
1100.1213	Single dose, 3-way crossover, bioequivalence of suspension vs. Tablet	NVP	1/97 - 3/97	21 adult volunteers
1100.1231	Single dose, 2-way crossover, bioavailability of suspension vs. Tablet	NVP	8/97 - 9/97	24 adults volunteers
Ongoing Studies				
1100.859	Expanded Access Program	NVP, NVP with other antiretrovirals	8/96 - TBD	19 children/naive and experienced
1100.892	Open-label, long term NVP access, pts from ACTG 180	NVP, NVP/ZDV, or NVP/ZDV/ddI	9/92 - TBD	29 children/experienced

4. Additional Information Requested by FDA.

The following published/unpublished manuscripts were not provided by the applicant initially with the supplement because most of them were studies of NVP used as single-dose regimens and were deemed by the applicant non-contributory to the safety database. The applicant later submitted these materials in response to FDA's request because the unique study population (neonates) was felt by this reviewer an important aspect to the safety profile of NVP as a whole. The four articles are:

- A. Mueller, BU et al. Comparison of virus burden in blood and sequential lymph node biopsy specimens from children infected with human immunodeficiency virus. *J. Ped.* 129: p.410-418, 1996. (ACTG 250)
- B. Mirochnick, M. et al. Pharmacokinetics of Nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. *J. Inf. Dis.* Vol. 178, p. 384-374, 1998.
- C. Musoke, P. et al. A phase 1 study of the safety and pharmacokinetics of Nevirapine in HIV-1 infected pregnant Ugandan women and their neonates. (Draft manuscript)
- D. Dorenbum-Kracer, A. et al. Antiretroviral use in pregnancy in PACTG 316: A phase 3 randomized, blinded study of single-dose intrapartum/neonatal nevirapine to reduce mother to infant HIV transmission. 12th World AIDS Conference, Geneva, Abstract no.23281.

Also in response to FDA's another request, the applicant submitted a list of post-marketing spontaneous reports of adverse events in children. To complement the applicant's database, a similar report generated by the Division of Pharmacovigilance and Epidemiology, FDA, is included in this review.

5. Review of Individual Studies

5.1 Trial 1100.882 (ACTG 180)

Title: Pharmacokinetics, safety, tolerance and activity of Nevirapine alone, in combination with ZDV, and in combination with ZDV and ddI in mildly to moderately symptomatic HIV-1 infected children

Comment: Although this protocol had an ACTG designation, the applicant was responsible for the monitoring and data management of the study.

5.1.1 Synopsis

This study was an open-label, multicenter study in which HIV-infected children were treated for 28 to 32 weeks of NVP 120 mg/m²/day for 28 days followed by NVP 240 mg/m²/day or 400 mg/m²/day for the remainder of the study.

During the trial, the design of the protocol were amended many times prompted primarily by the preliminary results from adult trials of NVP and changes in the treatment strategy of HIV infection at the time. Highlights of protocol changes are excerpted chronologically as below. (Source: Table 7.1.2, Vol. 88.1, page 34)

01/92:

Of the three daily dosing regimens (7.5, 30, 120 mg/m²), the two lower doses were dropped.

Reason: Based on resistance data from adult trials, NVP dose of 120 mg/m² appeared to be the best dose.

06/92:

Dose increased from 120 to 240 mg/m²/day.

Reason: Data became available indicating that the 240 mg/m²/day dose of NVP might produce a durable virologic response and prevent replication of resistance virus.

12/92:

All patients on NVP alone were eligible to receive ZDV after completing pk sampling.

Reason: To provide individual patients with alternative therapy based on clinical and laboratory data.

09/93:

NVP regimen was changed to 120 mg/m² bid for patients >9 years old and NVP dosage was increased to 200 mg/m² bid for patients ≤9 years of age.

Reason: Based on preliminary pk data, the change was made to increase NVP trough levels in patients of both age groups.

06/94:

10 new patients were to be enrolled and receive triple therapy (NVP/ZDV/ddI).

Reason: prompted by in vitro data and the state-of-art treatment strategy.

The primary endpoints of the study as described in the last version of revision were to evaluate NVP as monotherapy, double therapy, and triple therapy for the following parameters: safety and tolerance as measured by the incidence of adverse events; efficacy, as measured by changes from baseline in p24 antigen levels, in percent CD4+ cells and in weight-age and height-age percentiles over time; and pharmacokinetic parameters. It should be pointed out that the efficacy assessment was for an exploratory purpose.

To be included in the study, patients were to meet the following criteria:

- 1 day to ≤ 18 years of age
- serum p24 antigen (+) if <24 months; and serum p24 antigen ≥70 pg/ml if ≥ 24 months old
- required to have a CD4+ cell count as specified in the protocol and/or had mildly to moderately symptomatic HIV-1 infection
- If patient had a <6 weeks of ZDV or ddl therapy prior entry, a 7 day washout was required for the monotherapy group.

The following table lists the study drugs information used in this study.

Drug	Formulations	Dosage
NVP	Suspension (either 5 mg/ml or 10 mg/ml); tablets (2.5 mg, 12.5 mg, 50 mg, and 100 mg)	120 mg/m ² /day for the first 28 day lead-in, followed by either 120 mg/m ² bid or 200 mg/m ² bid.
ZDV	Tablet (100 mg) or syrup (10 mg/ml)	180 mg/m ² q6h or 240 mg/m ² q8h
ddl	Chewable tablet (50, 100 mg), solution (20 mg/ml)	100 mg/m ² q12h

As a general rule, children of age 2 months to <13 years received the liquid formulations, whereas children of age ≥ 13 years received the tablet formulations, but had the option of taking the liquid formulations if unable to take tablet.

Comment: The 28 lead-in dosing regimen for NVP was based on a previous trial experience that by exposing patients to NVP at a lower dose (200 mg daily) initially somehow reduced or eliminated the occurrence of a rash seen when patients were dosed with 400 mg daily without prior NVP treatment. While the mechanism is unknown, a plausible hypothesis is that pretreating patients with lower dose of NVP for 2 to 4 weeks to allow for full enzyme induction

(autoinduction) may avoid the high levels of either parent compound or metabolite that may be responsible for the rash events observed.

Of note is that a 28-day lead-in time was used in this study but a 14-day lead-in time was used in Study 1100.1032. Both periods are empirical and are probably equally appropriate since these reflect the period of autoinduction of NVP. However, the effectiveness of a 12-day lead-in time needs to be evaluated and supported by the full safety analysis of study 1100. 1032.

The pharmacokinetics of NVP was to be characterized utilizing a population pk approach. All adverse events, regardless of any suspected relationship to study drug therapy (i.e. NVP) were to record on the case report forms. For patients who prematurely discontinued from the study, adverse events with an onset date within 7 days of study discontinuation were considered to have occurred while the patient was 'on drug' and were included in the analysis.

5.1.2 Results

5.1.2.1 Disposition, Demographics, Extent of Drug Exposure

Thirty-seven (37) patients were enrolled into the study and received study therapy. The distribution of subjects in the three treatment regimen groups is shown in the table below.

Treatment Regimen	Total Number of Patients
NVP alone	11
NVP/ZDV	17*
NVP/ZDV/ddI	9

*10 of the patients who received double therapy began study treatment on monotherapy and added ZDV at some point during the study.

All 37 study patients had more than one protocol violation. The most frequently observed violations concerned incorrect timing of tests, missed assessments, and concomitant medications. Seven patients had one entry criterion violation, such as: had >6 weeks of ZDV therapy; no p24 antigen testing at study entry; abnormal lab data at baseline; and a p24 antigen value of 0. The applicant considered these protocol violations to be minor thus did not excluded these patients from the study and data analyses.

Baseline demographics and disease characteristics by treatment group are shown in the table below.

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	Number of Patients (%)			
	Mono	Double	Triple	Total
Total treated	11	7	9	37
Race				
White	2 (18%)	4(44%)	4(44%)	10(27%)
Black	3(27%)	6(35%)	1(11%)	10(27%)
Hispanic	5(46%)	5(29%)	4(44%)	14(38%)
Other	1(9%)	2(12%)	0	3(8%)
Sex				
Male	9(82%)	6(35%)	5(56%)	20(54%)
Female	2(18%)	11(65%)	4(44%)	17(46%)
Age (yr.)				
Median	8.3	0.8	0.2	0.9
Mean	8.1	1.8	0.4	3.3
Range	0.6-15	0.3-10.5	0.1-1.2	0.1-15
Weight (kg)				
Mean	29.8	11.3	6.4	15.6
Range	7.7-60	3.9-63.8	3.8-11.6	3.8-63.8
Height (cm)				
Mean	125	23.45	10	86.2
Range	64-174	50.8-148	46.5-76	46.5-174
HIV disease				
Asymptomatic	1(9%)	2(12%)	4(44%)	7(19%)
Symptomatic	10(91%)	15(88%)	5(56%)	30(81%)

Source: _____

The above table shows that the average age was younger for the double and triple therapy groups than for the monotherapy group. Eighty-one percent (81%) patients enrolled were symptomatic at entry.

The types of NVP drug formulations administered to these 37 patients are shown in the table below.

Suspension			Tablet	Total no. of patients
10-ml	5-ml	Both		
22	7	4*		33
			4	4

* 1 also received tablets.

As shown above, 89% (33/37) received the suspension formulation of NVP in this trial.

Comment: The NVP oral suspension has a high viscosity. Since a majority of patients received NVP suspension in the trial, the degree of completeness of the

intended volume of the suspension actually consumed by children is crucial to a pk determination, particularly in children of very young age when the required volume of the suspension was small.

As described in the protocol, instructions for administration were quite cumbersome and might have not been complied by some patients. Depending on the volume required, either a 1 or 5-ml size syringe would be used to draw up the required volume and then expelled it and the drawing-expelling was repeated a couple of times to coat the syringe prior to administering to patients. For volume larger than 5 ml, a shallow spoon could be used. Of note is that there was no mentioning of using a dose cup.

A laboratory study (AS970024, NDA 20-636, vol. 37.3 page 376) conducted by the applicant to determine the amount of drug product residue remain in the plastic dose cups was prompted by a failed bioequivalence study (Study 1100.1213) in which plastic dose cups were used by the participants. (Please refer to Dr. Sekar's review for discussion.) The results of this laboratory study confirmed that a significant amount of NVP suspension (8.6 to 11.6%) remained as a residue in dose cups when administered without a wash-out of the cup with water.

Another concern for the subtherapeutic levels of NVP resulted from underdosing is the possibility of HIV isolates resistance .

In view of the preceding discussion, a description of the method of administration is needed for the package insert of NVP oral suspension.

The intended duration of the study was 6 months, which was extended to 211 days for patients receiving double therapy (Amendment no. 2) and 224 days for patients receiving triple therapy (Amendment no.8). Additionally, patients who completed 168 days of NVP therapy were allowed to continue on this trial until they could enter the long-term follow-up trial 1100.892 (Amendment no. 5).

Because participants in the trial were allowed to switch dosing of NVP during the trial, therefore, a patient could be counted twice when the extent of exposure to NVP expressed by dose was described. For example, patient #621 received 120 mg/m²/day for 3 months followed by 240 mg/m²/day for 2 months. Patient #621 was counted twice under the exposure by dose received: 120 and 240 mg/m²/day respectively; however the same patient was counted only once under the total exposure of >3 - 6 months.

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Total period of exposure (month)		No. of patients			
		≤ 120 mg/m2/d	240 mg/m2/d	400 mg/m2/d	Total exposure
> 0-1	No. of pts	21	4	0	1
>1-3	no. of pts	8	6	2	0
>3-6	no. of pts	4	6	6	8
>6-9	no. of pts	0	4	15	23
>9-12	no. of pts	0	0	0	5
Total	no. of pts	33	20	23	37
	Mean	1.52	3.65	6.03	7.08
	Min	0.53	0.13	1.35	0.72
	Max	5.52	8.97	8.97	11.47

The above table indicates that the mean duration of exposure (regardless of dose) for the 37 patients enrolled in this study was 7.08 months, with a range of 0.7 to 11.5 months. Twenty-eight of the 37 patients (76%) were treated for more than 6 months.

5.1.2.2 Efficacy Analyses

In this review, no attempt was made to reanalyze the applicant's efficacy data as normally would be done for NDAs. This is due of two reasons: first, efficacy of NVP was not the primary objective in the study design, second, methodologies for measuring the levels of p24 antigen, HIV-RNA and percent CD4+ cells were developed at different time during the trial, consequently, not all activity measures were performed for all patients at all visits. The purpose of this review is to document that the activity of NVP shown by HIV-infected children in this trial is in the same direction as that shown by adults.

5.1.2.2.1 p24 Antigen

The ICD p24 antigen (immune complex dissociated) was assessed for 28 patients. The HIV-1 Antigen Assay was employed.

Results of p24 Antigen over time and % of patients with p24 levels that returned to baseline are shown in the table below.

Regimen (# pts)	Median p24 (pg/ml)	Median % change (p-value)*					% (#) pts with p24 returned to baseline
		wk 2	wk 4	wk 8	wk 12	wk 24-28	
NVP (n=8)	646	-56(0.04) n=8	-21 (0.02) n=7	-24(0.30) n=7	+4(0.81) n=7	+60(0.63) n=4	75% (6 of 8)
NVP/ZDV (n=16)	1427	-69(<0.01) n=11	-37(0.01) n=11	-39(0.30) n=12	-15(0.49) n=10	-62(1.00) n=7	38% (6 of 16)
NVP/ZDV /ddI (n=4)	1032	-88(0.13) n=4	-96(0.25)n=3	-90(0.25) n=3	-87(0.50)n=2	-94(0.25) n=3	0% (0 of 4)

* using Wilcoxon signed-rank test

The above table shows that treatment with NVP, used as either monotherapy or double therapy, produced a 'statistically significant' decrease from baseline in the median percent change of p24 antigen levels for the first 4 weeks of therapy. By week 8, the difference was no longer significant, and by week 12, the median value for monotherapy patients had risen above baseline. Although treatment with triple therapy produced a higher level (96%) of reduction in median p24 antigen level at week 4 and maintained for 24 weeks, this result was not statistically significant due to the small sample size. The p24 antigen level returned to baseline in 75% of patients treated with NVP alone and in 38% of patients treated with NVP/ZDV by the end of the study but none in the triple therapy group who were evaluated had p24 values that returned to baseline.

Comment: Only few studies have attempted to follow antiviral efficacy using the ICD p24 antigen level assay. However, when this protocol was designed (1991), ICD p24 antigen assessment was deemed useful to screen potential therapeutic regimens.

Results of p24 antigen level measurement show that the effect of NVP treatment on p24 surrogate marker is short-lived in pre-treated children whether NVP was used as monotherapy or in combination of NVP and ZDV or NVP and ZDV + ddI.

5.1.2.2.2 HIV-1 RNA levels

Since the HIV-RNA assay was developed and instituted after the trial had begun, none of the monotherapy patients were tested for HIV-RNA levels. HIV-RNA was assessed for 16 patients. _____) was employed. This test has a limit of quantification of _____

The results of median absolute change in HIV-RNA over time and percent of patients with HIV-RNA levels that returned to baseline are shown in the table below.

Regimen(#pts)	Median baseline HIV-RNA(Log ₁₀ copies/ml)	Median change in Log ₁₀ HIV-RNA (p-value)					% (#) patients with HIV-RNA levels returned to baseline
		Wk 2	Wk 4	Wk 8	Wk 12	Wk 24	
NVP/ZDV (n=8)	5.64	-0.72(0.02) n=7	-0.11(0.69) n=6	-0.08(0.81) n=5	-0.15 (0.11) n=7	0.14(0.47) n=7	75% (6 of 8)
NVP/ZDV/ddI (n=8)	5.48	-1.77 (0.02) n=7	-2.10(0.06) n=5	-2.24 (0.03) n=6	- 0.88(0.01) n=8	-1.23 (0.03) n=7	13% (1 of 8)

The above results indicate that patients treated with NVP/ZDV/ddI maintained a median decrease of greater than 2 logs below baseline in HIV-RNA levels for 8 weeks. Only 1 of eight patients treated with triple therapy had HIV-RNA levels that returned to baseline.

Of interest, two patients who received triple therapy achieved readings below the limit of quantification (BLQ) on day 161 (last observation) for one patient and day 55 and remained BLQ for the length of the trial (through day 223) for the second patient. As described in the publication of the study¹, longer follow-up of both patients was undertaken and plasma samples from these infants were also studied by an ultrasensitive assay with a detection limit of: [redacted]. The plasma HIV-1 RNA levels were again BLQ at 16 months and 18 months of therapy respectively.

Comments: Although there were no resistance data included in supplement, the issue of viral resistance was discussed in the same publication as cited in footnote #1. All the HIV-1 isolates from the 8 patients before receiving triple therapy were sensitive to NVP. Viruses with decreased sensitivity to NVP were isolated during the treatment period from 5 patients (not including the 2 infants who had made the goal of 'undetectable' levels). The viral resistance results for this small pediatric cohort were similar to that observed in adults.

Although the sample size of the patients receiving a triple regimen was small, there are several notable differences between the results in children and that of ACTG 241 (adults). The median baseline HIV-1 RNA level was higher in the pediatric trial than the adult trial (5.48 vs. 4.59 log₁₀ copies /ml), and the magnitude of viral load reduction is greater in this pediatric trial than that in the adults (2.24 vs. 1.15 log₁₀ reduction).

5.1.2.2.3 Percent CD4+

The results of median absolute change in percent CD4+ cells over time are shown in the table below.

Regimen (#pts)	Median baseline % CD4+	Median absolute change in % CD4+(p-value)			
		Wk 2-4	Wk 8	Wk 12-16	Wk 24-32
NVP (n=10)	28.5	0.5 (0.94) n=8	0.5(0.03) n=9	3.0(0.20) n=9	1.3(0.05) n=8
NVP/ZDV (n=17)	20.0	5.0(<0.01) n=15	4.5 (0.01) n=15	9.5(0.04) n=14	12.0(0.02) n=10
NVP/ZDV/ddI (n=9)	38.5	2.0(0.75) n=9	4.5(0.22)n=7	7.5(0.22) n=7	3.8 (0.67) n=8

The above results show that patients in all three treatment regimens maintained a median increase above baseline in percent CD4+ cells for 24 to 32 weeks. This trend was similar to that observed in adults.

¹ Luzuriaga, K, et. Al. Combination treatment with zidovudine, didanosine, and nevirapine infants with human immunodeficiency virus type 1 infection. N. Eng. J. Med. 136: 1343-1349, 1997.

5.1.2.2.4 Weight

The results for changes in the median absolute values for weight-age percentile over time are shown in the table below.

Regimen (#pts)	Median baseline wt-age percentile	Median absolute change in wt-age percentile (p-value)					
		Wk 2	Wk 4	Wk 12	Wk 16	Wk 24	Wk 32
NVP (n=11)	55.1	+2.0 (0.19) n=11	-1.0 (0.65) n=10	+0.0 (0.74) n=9	-0.6 (0.32) n=11	+0.6(0.58)) n=8	+2.4 (0.63) n=4
NVP/ZDV (n=17)	7.8	0.0(0.61) n=17	0.0(0.71) n=15	0.0(0.95) n=16	0.0(0.22) n=16	0.0(0.6) n=15	+0.5(0.44))n=5
NVP/ZDV/ddI (n=9)	36.6	+6.4 (0.05) n=9	+10.7 (0.01) n=9	+10.4 (0.04) n=9	+9.3 (0.15) n=8	+9.9(0.04)) n=8	+15.1 (0.08) n=8

Neither the mono- nor double therapy group showed a change from their baseline weight-age median percentiles. Treatment with NVP/ZDV/ddI resulted in a 20.7% increase by week 4. At baseline, the median weight-age percentile for this group was 37% (below average relative to the international growth reference population). The 15-point increase after 32 weeks of triple therapy resulted in these patients reaching an average weight-age percentile (52%).

The applicant did a subgroup analysis and concluded that the increases in weight-age index observed in the triple therapy group did not appear to be a function of patient age (analysis not included in this review.)

5.1.2.2.5 Summary of Efficacy

The applicant concluded that in this study of 37 HIV-infected pediatric patients with 6 weeks or less of prior nucleoside therapy, there was an initial virologic and immunologic response to treatment with all NVP regimens: monotherapy, double therapy with ZDV, or triple therapy with ZDV and ddI. Analysis of data for p24 antigen levels, HIV-RNA levels, percent CD4+ cells, and weight-age growth index suggested that treatment with triple therapy gives the most consistent improvement relative to baseline.

Comment: Results of this trial demonstrate that NVP is active on surrogate markers in pre-treated children. However, no definitive conclusions can be made owing to the small sample size.

5.1.2.3 Safety Analyses

5.1.2.3.1 Summary of Safety Profile of NVP in Adults

The safety profile of NVP in 252 adults presented in the original NDA shows that the major toxicity of NVP is a maculopapular rash on the face, trunk and extremities, which may be accompanied with fever and usually has an onset within the first 28 days of treatment. The overall incidence under the labeling recommended dosing regimen was 17% with 7.6% reaching grade 3 or 4 on the ACTG toxicity scale. There were 3 cases of Stevens-Johnson Syndrome (SJS) reported in the adult trials. Nineteen (19) additional cases of NVP-associated SJS or Toxic Epidermal necrolysis (TEN) have been reported to the FDA since NVP's approval in 1996.²

Nevirapine has been reported to be associated with elevated gamma-glutamyl-transpeptidase (GGT), fever, nausea, and headache.

5.1.2.3.2 Safety Analyses in Children

For the applicant's analyses, the following rules were followed:

- If a patient experienced a specific event more than once, the events were classified by their maximum intensity. Causality (i.e., relationship to NVP) was judged by the investigator.
- If a double therapy patient experienced an adverse event while ZDV had been interrupted this would be listed in the NVP monotherapy tables. Therefore the total number of patients in the monotherapy tables is greater than the number of patients who were actually enrolled in the monotherapy group.
- Patients may have also experienced events while taking different doses during the trial; therefore, the sum of patients who experienced a given event listed under individual dosing regimens may exceed the number of patients in the 'Total' column of summary tables in which individual patients are only counted once.

The overall incidence of patients with adverse events by treatment is presented in the table below.

Treatment Group	NVP Dose/# Pts (%)			Total
	≤120 mg/m ² /d	240 mg/m ² /d	400 mg/m ² /d	
MONOtherapy	n=17	n=19	n=12	n=27
All causality	17(100%)	18 (95%)	10 (83%)	25 (93%)
NVP related	8(47%)	4(21%)	3(25%)	13 (48%)
DOUBLEtherapy	n=7	n=7	n=14	n=18
All causality	6(86%)	6(86%)	13 (93%)	18 (100%)
NVP-related	1(14%)	0	4(29%)	4(22%)
TRIPLEtherapy	n=9	n=0	n=8	n=9
All causality	6(67%)	-	8(100%)	9(100%)
NVP-related	2(22%)	-	1(13%)	2(22%)

Source: _____ 1:1

The above table shows that the highest percentage of patients with NVP-related adverse events was observed in the monotherapy group (48%) as compared to 22% in the double or triple regimen group.

² Warren, KJ, et al. Nevirapine-associated Stevens-Johnson syndrome. *Lancet*, 351: p 567, 1998.

hepatomegaly, one of which was considered possibly related to NVP. None experienced hepatitis in this trial.

Twenty-three patients (62%) had clinically important abnormalities in LFTs (SGPT, SGOT, GGT, alkaline phosphatase, total bilirubin). Two patients had clinically important increases in GGT values (5%). Three patients had SGPT increases (8%). Most of them were elevations in alkaline phosphatase only (19 patients, 51%). Elevated levels of alkaline phosphatase gradually declined in most patients at the last visit and none of these patients required NVP interruption.

Comment The results of trial 1100.882 show that the incidences of GGT or SGPT elevations are comparable between children and adults (in adults, GGT elevation occurred in 6.3%; SGPT elevation occurred in 9%), however, the incidence of alkaline phosphatase elevation was disproportionately more frequent in this trial. The applicant attributed the alkaline phosphatase level elevations to normal growth in children.

An FDA's review of the data revealed the following:

Of the 19 patients with clinically important increases in serum alkaline phosphatase levels, only one patient had a parallel rise in GGT.

There were two patterns of elevation profiles:

- Elevations fluctuated between Grade 1 and 2 during the trial (levels around 236 u/L).⁵
- Elevations fluctuated between Grade 1 and 2 during the trial with 'spurs' of Grade 4 elevations (≥ 1000 U/L), i.e. usually return to Grade 2 on the very next measurement.

Since none of these 19 patients with abnormal alkaline phosphatase levels were associated with other adverse events and non required NVP interruption, this reviewer agrees with the applicant's interpretation that alkaline phosphatase elevations are likely a reflection of normal growth in children. However, the issue of alkaline phosphatase elevation should be revisited when the full analyses is completed for ACTG 245.

5.1.2.3.4 Summary of Safety

In general, the safety profile of NVP in children is similar to that in adults. Sixteen percent (16%) of patients had rashes that were considered by the investigator to be NVP related; this is identical to the incidence of rash attributed to NVP observed in adults trials. Granulocytopenia was not observed as one of the most common drug related events in adults but was observed in 5 patients in this trial. Although the applicant considered the event could be related to ZDV component of the treatment regimen, one of the five patients received monotherapy with NVP. There was a high rate of increased

⁵ Normal range of alkaline phosphatase levels used in this trial was 39-113 U/L.

alkaline phosphatase(51%) observed in this trial. The applicant attributed this high rate to normal growth in children.

NVP appears to be well tolerated in this study where the drug exposure ranged from 0.7 to 11.5 months.

5.2 Trial 1100.892

Title: A long-term open-label trial assessing safety and tolerance of chronic NVP doing in HIV-infected children

Comment: An inconsistency between the original protocol and applicant's synopsis of this trial was noted. In the original protocol, assessing the safety and tolerance of NVP dosing was stated as the primary objective of the study whereas assessing durability of virological and immunological changes was stated the secondary objective. The synopsis, however, made no reference to virological/immunological assessments, nor was it evident that such data had been actually collected during the trial.

5.2.1 Synopsis

The study began enrollment in 1992 and is still ongoing. Like study 1100.882, depending on the timing of enrollment, patients could access NVP alone, NVP and ZDV in double combination, or NVP,ZDV, and ddI as a triple combination regimen. At the time of study entry, the respective number of patients receiving mono-, double-, or triple regimen of NVP were 9, 13, and 7. By the end of their participation, more patients were switched to the triple regimen; the respective numbers were 1, 6, and 22.

The NVP dosing regimen was identical to that used in previous trial.

For patients receiving NVP alone or NVP and ZDV, visits were to be made at monthly interval from week 4 through 24 followed by quarterly visits. For patients receiving triple therapy, a closer monitoring schedule was designed. Visits were to occur on study day 0, bimonthly for 6 visits, at monthly intervals for the next three visits, and at quarterly intervals thereafter.

Assessments at each visit consisted of the following: vital signs, height, weight, and head circumference if <2years of age, physical and neurological examinations, HIV-1 signs and symptoms, adverse events, routine lab tests, specimens for NVP trough plasma levels and ZDV trough plasma levels, if applicable. (Note the absence of virological/immunological measurements)

5.2.2 Disposition, Demographics and Extent of Drug Exposure

As of 01 June 1997, CRFs for 29 patient who entered Trial 1100.892 were received at BIPI.

The following table provides a summary of the patient demographics.

Characteristic	No. of Patients (n=29)
Mean age (year)	4.4
Range	0.8 -15.6
Gender: Male/Female	16/13
Race	
White	10
Hispanic	9
Black	7
Other	3
Mean weight (kg)	19.9
Range (kg)	6.5 - 63.5
HIV disease status	
Aymptomatic	5
Symptomatic	24

The extent of exposure to NVP for subjects in Trial 1100.892 is presented in the following table.

Total period of exposure (months)		Mg/m2/day			
		≤120	240	400	total
>0-1	No. of pts	1	0	0	0
>1-3	No. of pts	1	1	1	1
>3-6	No. of pts	0	3	2	2
>6-9	No. of pts	0	1	2	2
>12 -24	No. of pts	0	2	10	11
>24 -36	No. of pts	0	0	6	3
>36	No. of pts	0	6	1	10
Total	No. of pts	2	13	22	29
	Mean	1.25	25.59	19.92	26.67
	Min	0.92	1.45	1.15	1.15
	Max	1.58	55.62	36.59	55.62

Source: Table 3.1, vol.37.5, p.33

Similar to Trail 1100.882, patients may have changed their NVP dose throughout study. Hence, the total of the patients in each treatment group is greater than the grand total of patient in the trial.

The mean duration of NVP exposure for the 29 patients enrolled in the study was 26.67 months [2.2 year, with a range of 1.2 to 55.6 months (0.1 to 4.6 years)]. Most of these patients (24/29, 83%) received NVP for greater than 1 year.

Before entry into Trial 1100.892, the 29 patients had participated in Trial 1100.882 for approximately 6 to 11 months. The mean duration of total NVP exposure, combining exposure for Trial 882 and Trial 892, for the 29 patients enrolled in the study was 33.9 month (2.8 year) with a range of 6.8 to 63.5 months (5.3 year).

Comment: While the majority of patients (27/29, 93%) entered into trial 1100.982 without any interruptions of antiretroviral treatment from previous trial, two patients' antiretroviral therapies were interrupted for 28 days and 40

days respectively. Interestingly neither patient restarted a new round of lead-in NVP dosing nor did either one report to have a rash event during the trial.

5.2.3 Efficacy Analyses

None provided.

5.2.4 Safety Analyses

Since that the overall adverse events profile was not dissimilar to that observed in the previous trial, and that similar events could be recurring or continuing from the previous study, this section of review will not include the entire safety data, instead only focuses on the occurrence of events that were observed for the first time during this trial.

Rash:

Three cases of rash events were considered NVP-related, patient # 542, 621, and 646, all were mild to moderate and resolved after 2, 62 and 4 days respectively. NVP therapy was interrupted in patient 646 only.

Laboratory Abnormalities:

Three patients experienced clinically important elevated LFTs: patients # 1702, 1742 and 1722. All had normal or Grade 1 level of LFTs at the last visit in Trial 1100.882. Patient 1702 and 1742 had clinically important elevations in SGOT up to Grade 3 levels which fell to Grade 1 on further observations for these tests. Patient #1722 had a transient elevation in total bilirubin to a Grade 3 value. The only patient discontinued NVP dosing due to laboratory abnormalities was patient #1742 who had a grade 4 anemia and pancytopenia.

Deaths:

Two patients died during the trial: one died of pneumococcal sepsis and the other died of pancytopenia. In both cases the investigator considered the events were unrelated to NVP.

The applicant concluded that pediatric patients who tolerated NVP for approximately 6-11 months in the previous trial continued to tolerate NVP well in longer-term exposure for up to an additional 4.6 years.

Comment: The applicant's conclusion is reasonable.

5.3 Trial 1100.1032 (ACTG 245)

Title: A Comparative Study of Combination Antiretroviral therapy in Children and Adolescents with HIV Disease

This trial was sponsored and monitored by the DAIDS.

5.3.1 Abbreviated Study Report

In this report, only serious adverse events were included.

This Phase I/II randomized, double-blind, placebo-controlled trial compares two double therapy regimens (ZDV/ddI or NVP/ddI) and one triple therapy regimen (NVP/ZDV/ddI) in patients ages 6 months to 20 years old.

NVP was started with a lead-in dose of 120 mg/m²/day for 2 weeks and then escalated to 120 mg/m²/bid thereafter. The total daily dose of NVP was not to exceed 400 mg/day. ZDV was given at a dose of 180 mg/m² tid and ddI was given at a dose of 100 mg/m² bid.

Comment: The 2-week lead-in dosing period is shorter than that was used in trial 1100.882 but is what has been recommended in the package insert of VIRAMUNE for adult use. Whether a 2-week is better or same as a 4-week lead-in period with respect to the incidence of rash event in children remains to be seen.

During the course of the trial, a total of 225 patients received NVP suspension: 105 patients received NVP tablets, and 25 received both formulations. The distribution for both formulations according to treatment groups is shown in the table below.

	Number of Patients		
	NVP/ZDV/dd I	NVP/ddI	Total NVP treatment groups*
# Pts treated with NVP suspension	116	109	225
# Pts treated with NVP tablet	50	55	105

Patients may have received both tablets and oral suspension. Therefore the total number of patients is greater than the total number treated.

The intended duration of treatment was 48 weeks. Patients who completed 48 weeks of therapy had the option to continue on their blinded randomized treatment regimen until the last patient enrolled had received 48 weeks of therapy. Patients could continue on a blinded study extension for an additional 16 weeks.

The safety report, prepared by BIPI, evaluated only serious adverse event data for all patients through a data cut-off of 01 August 1997 for both the comparative portion of the trial and the study extension. Serious adverse events included Grade 3-4 rash events, hepatitis events and events that the ACTG reported as 10-day IND safety reports. Information on extent of drug exposure, adverse events leading to withdrawal, clinically important laboratory changes, concomitant medication etc were not available at the filing of this supplement.

According to the applicant, the investigators assessed causality of serious adverse events in different ways. In some cases, causality specifically referred to the entire regimen and in others referred to only NVP. Therefore, the applicant chose a conservative approach,

i.e., events that were recorded as related to the study regimen were handled as possible NVP-related events.

In this submission, summaries of NVP-related serious adverse events, all serious adverse events regardless of causality, and a summary of all fatal events were presented. Serious rash events, serious hepatic events, and events that the ACTG reported as 10-day IND safety reports were discussed. A blinded assessment of relationship to study drugs for all serious events was made by the investigator, DAIDs medical officer, and a BIPI physician.⁶ Of note, since DAIDs is performing the data management for this trial, BIPI has not been able to clarify minor discrepancies that exist in the serious adverse event data listings and clinical narratives.

Although 432 patients were enrolled in the trial, one patient discontinued before the trial medication was administered. Data for all 431 patients who participated in the comparative portion of the trial and the study extension and for whom data were received by BIPI as of 8/1/97 were included in the safety database.

5.3.2 Patient Demographics

Patient demographics are shown in the following table.

	Number of patients (%)			
	NVP/ZDV/ddI (n=154)	NVP/ddI/ZDV pla (n=151)	ZDV/ddI/NVP pla (n=126)	Total (n=431)
Age(yr.) Mean	7.5	7.2	7.8	7.5
Range	0.8-18.5	0.9-19.3	0.8-16.8	0.8-19.3
Gender: Male	98(58%)	90(60%)	74(59%)	254(59%)
Female	64(42%)	61(40%)	52(41%)	177(41%)
Race: African American	59(38%)	69(46%)	56(44%)	184(43%)
Hispanic	59(38%)	56(37%)	49(39%)	164(38%)
Caucasian	35(23%)	24(16%)	21(17%)	80(19%)
Unknown	1(0.6%)	2(1%)	0	3(0.7%)

Source: vol 37.4, p. 23, Table 1.1

As shown above, the three treatment groups were well balanced in regard to age, sex, and race.

5.3.3 Incidence of Serious Adverse Events (Grade 3-4)

The overall incidence of patients with serious adverse events by treatment regimen is shown in following table.

Type of serious adverse events	Treatment group/# pts (%)			
	NVP/ZDV/ddI (n=154)	NVP/ddI (n=151)	ZDV/ddI (n=126)	Total of combined NVP groups (n=305)

⁶ Since causality assessment was performed without the knowledge of treatment group, a few serious events were documented to be NVP-related in the ZDV/ddI treatment group (NVP placebo).

All causality	36(23)	46(31)	37(29)	82(27)
NVP-related	12(8)	18(12)	5(4)	30(10)

Source: vol. 37.4, page 13, Table A.

At least one serious adverse event, regardless of causality, was reported for 23% of patients in the triple therapy NVP group and 31% of those in the double therapy NVP group compared to 29% of those in the ZDV/ddI group. At least one drug-related event was reported for 8% of the NVP/ZDV/ddI group, 12% of the NVP/ddI group, and 4% of the ZDV/ddI group.

Incidence of all causality serious adverse events reported in $\geq 2\%$ of patients is shown in the following table.

Adverse Event	# of patients (%)							
	NVP/ZDV/ddI (n=154)		NVP/ddI (n=151)		ZDV/ddI (n=136)		Total NVP groups (n=305)	
	All Causality	NVP-related	All Causality	NVP-related	All Causality	NVP-related	All Causality	NVP-related
Total serious events	36(23%)	12(8%)	46(31%)	18(21%)	37(29%)	5(4%)	82(27%)	30(10%)
Rash ⁷	3(2)	2(1)	8(5)	7(5)	1(1)	1(1)	11(4)	9(3)
Fever	8(5)	4(3)	7(5)	3(2)	3(2)	1(1)	15(5)	7(2)
Granulocytopenia	4(3)	2(1)	3(2)	3(2)	3(2)	0	7(2)	5(2)
Anemia	4(3)	1(1)	4(3)	2(1)	2(2)	1(1)	8(3)	3(1)
Thrombocytopenia	2(1)	1(1)	3(2)	1(1)	2(2)	1(1)	5(2)	2(1)
Pancreatitis	1(1)	0	1(1)	1(1)	2(2)	1(1)	2(1)	1(0.3)
Pneumonia	7(5)	1(1)	6(4)	1(1)	10(8)	0	13(4)	2(1)
Vomiting	3(2)	0	3(2)	2(1)	2(2)	0	6(2)	2(1)
Abdominal pain	3(2)	2(1)	0	0	3(2)	0	3(1)	2(1)
Nausea	2(1)	1(1)	1(1)	0	2(2)	1(1)	3(1)	1(0.3)
Cardiomyopathy	5(3)	1(1)	1(1)	0	0	0	6(2)	1(0.3)

Source: Vol 37.4, page 14, Table B.

The most commonly occurring serious adverse events in the combined NVP treatment groups that were considered at least possibly related to NVP by the investigators were rash (3%), fever (2%) and granulocytopenia (2%).

The incidence of serious adverse events in the triple therapy NVP group was similar to the double therapy NVP group.

5.3.4 Case Report Forms Included in the Submission

The topic of CRF was brought up several times between the applicant and the Division. At issue was the scope of CRFs that FDA clinical reviewers deemed necessary for a proper review. At the pre-NDA meeting, the Division had requested, for ACTG 245, CRF's for all drug-related deaths, rashes greater than or equal to grade 2 in severity and for a sample of serious adverse events be submitted.

⁷ Rash events include the following terms: rash, erythematous rash, maculopapular rash, erythema multiforme, Stevens-Johnson syndrome, Stevens-Johnson/toxic epidermal necrolysis transition syndrome, allergic reaction with rash, anaphylaxis with mild rash.

Instead, the applicant later proposed to include only 14 patients whose adverse events were determined by the applicant to be of most medically important and added that "any additional CRFs requested for submission with the pediatric supplement will likely delay the submission." The Division, based on the list provided by the applicant in a correspondence dated 1/12/98 (serial no. 290), made an additional request for CRFs from 6 patients who had presented rash as a serious adverse event.

In the end, there were a total of 20 CRFs included in the supplement; 14 of which, selected by the applicant, were submitted in 3/98, whereas the other 6, selected by the Division, were submitted in 5/98.

In addition, the applicant presented clinical narratives for 60 selected patients. The inclusion of a narrative for a patient was based on the these criteria: expedited reports for events there were at least possibly related to study drug; a serious adverse event that had an outcome of death; a serious adverse event that was possibly related to NVP and resulted in study drug discontinuation; and Stevens Johnson syndrome, Grade 3/4 rashes, hepatitis, and Grade 3/4 LFTs elevation.

Although most of the reported serious adverse events were classified as possibly NVP-related by the investigator, such association with NVP was largely discounted upon the applicant's reevaluation. Of note, applicant's evaluation was not based on patients' medical records (since medical records have not been made available to BIPI.). The following table summarizes the agreement/disagreement of assessments between investitgator's (PI) and the applicant's (BI) for the 60 selected narrative case reports.

Agreement		Disagreement	
Not NVP-related ⁸	32	NVP-related by PI ⁹	16
NVP-related ¹⁰	11	NVP-related by BI ¹¹	1
Total = 43		Total = 17	

In general, the above table suggests that the applicant had a preconceived notion that, with the exception of rash and SJS, all other adverse events were most likely not related to NVP. Since, after all, only investigator's assessment was used in the analysis, no further investigation into this discrepancy is felt necessary at this point.

5.3.3 Specific Events

Despite the incompleteness of the safety database and a lack of proper documentation for verification, the rash and hepatic events (even incidence < 2%) are felt significantly important to be reviewed in more detail.

⁸ AIDS, diarrhea, encephalopathy, respiratory distress, PCP, bacterial infection etc.

⁹ Thrombocytopenia, ataxia, nephritis, neutropenia, abdominal pain, anemia etc.

¹⁰ SJS, rash, fever

¹¹ Fever

Rash:

Patient ID	Rash description	Treatment Group	Onset days	Relationship to NVP12	Other comments	Action with NVP
230928	SJS?TEN	NVP/ddI	23	Possible	Otitis media, fever	Discontinued
500960	SJS	NVP/ddI	25	Possible	Pruritus, fever	Discontinued
300348	Anaphylaxis with rash	NVP/ddI	21	Definite	Fever, pruritus, hives	Discontinued
280417	Erythema multiforme	NVP/ddI	337	Doubtful	Fever	Interrupted
300302	Rash maculopapular	NVP/ddI	8	Possible	Fever, edema face	Discontinued
410066	Rash	NVP/ddI	11	Possible	Fever	Discontinued
501314	Rash erythematous	NVP/ddI	190	Possible	Angioedema, maculars, papulars, vesicles	Unknown
501327	Rash	NVP/ddI	2	Possible	No lead-in dosing	Dose reduced
690015	Rash erythematous	NVP/ZDV/ddI	9	Possible	Fever	Discontinued
690209	Allergic reaction with rash	NVP/ZDV/ddI	1	Definite	Tachycardia	Discontinued
410337	Allergic reaction with rash	NVP/ZDV/ddI	142	Doubtful	Fever, edema, dapsone-related ?	Continued

Source: Vol. 37.4, page 16, Table D.

Nine of these patients experienced rashes that were considered related to NVP treatment by the investigator. Eight of these events occurred in the first 6 weeks of NVP treatment when most NVP-related rashes have been shown to occur in adults. There were two observations which have not been previously observed in adults. 1. Two rashes occurred very early in treatment (1 to 2 days). Of note is that one of the patients who experienced rash did not utilize the lead-in dosing period. 2. Three rash events were accompanied by allergic reactions characterized by anaphylaxis, facial edema and tachycardia. Since this database was limited to 'serious' events, the full extent of these two observations in pediatric population can not be appreciated.

**APPEARS THIS WAY
ON ORIGINAL**

Two NVP-treated patients (0.7%) experienced SJS or SJS/TEN. This incidence is slightly lower than that reported for adult trials (1.1%, 3/252).

Hepatic Serious Adverse Events:

Patient ID	Treatment Group	Onset Days	Relationship to NVP	Other Comments	Event Outcome
290014	NVP/ddI	193	Doubtful	Hepatic failure	Fatal
300302	NVP/ddI	368	Doubtful	Hepatitis C	Fatal
400182	NVP/ddI	14	Possible	Elevated Alk-p, GGT, hepatomegaly	Unknown
730215	NVP/ZDV/ddI	635	Doubtful	Hepatomegaly	fatal

Source: Vol. 37.4, page 71, Listing 2.2.

The applicant disagreed with the investigator on patient 400182's assessment. Since this patient had a history of elevated alkaline phosphatase, GGT, and endoscopic retrograde cholangiopancreatography findings suggestive of cholangitis prior to beginning study therapy, the applicant judged the events to be not related to NVP.

Comment: Based on FDA's review of this patient's CRF, the applicant's reevaluation is reasonable.

Deaths:

There were 48 deaths in the study as of 8/1/97. Of all fatal cases, 12 patients (8%) were in the NVP/ZDV/ddI group, 22 patients (15%) were in the NVP/ddI group and 14 patients (11%) were in the ZDV/ddI group. The most common fatal events were AIDS, pneumonia, PCP, respiratory insufficiency, cardiac failure, and cardiomyopathy. None of these fatal events were considered to be NVP-related.

The applicant therefore concluded that the serious adverse event profile of NVP in nucleoside-experienced children (10 months to 19 years of age) with advanced HIV-infection was similar to that observed in adults. No new adverse events were identified.

Comment: With a sample size of 431 enrolled in a randomized and placebo-controlled trial, ACTG 25 is perhaps one of few major pediatric HIV trials ever undertaken. Since included in this supplement is a partial study report, the safety profile, in its broadest sense, can not be fully appreciated. It is hoped that the study, when fully analyzed, will be able to address the following issues:

- The efficacy of double and triple regimens of NVP as measured by surrogate markers
- The appropriateness of a 2-week lead-in dosing regimen based on the incidence of rash events.
- The characteristics of rash occurrence in children including the onset and accompanied symptoms and signs (such as allergic reactions)

- The incidence of hepatic adverse events and the significance of the alkaline phosphatase elevations in this study population.

5.4 Other Trials

5.4.1 Trial 1100.895

This expanded access trial was open for enrollment for adults and children in May 1996. Only the pediatric patients enrolled in this trial were submitted. Subsequent to FDA approval of NVP in the U.S. for the treatment of HIV-1 disease in adults in June 1996, trial 1100.859 was closed to accrual for adults, but the trial remains open for pediatric patients.

Comment: The study is not deemed contributory to the safety database as a whole due to the following reasons:

- The study was of poor quality. CRFs were received directly from investigators without on-site monitoring. Some data issues have not been resolved. For example, one patient was treated in this trial without proof of HIV-infection.
- NVP dosing information was missing for some patients.
- The investigator documented only those adverse events that were judged to be related to NVP. A total picture of the incidence of adverse events (all causality) can not be appreciated for this trial.

6 Literature

Per FDA's request, the applicant submitted on 07/16/98 the manuscripts of four NVP studies in children. The safety data contained in each publication were either lacking or very limited as shown in the table below.

Authors	Study Description	Subjects	Treatment	Adverse Events
Mueller, BU et al.(NCI), completed	Virus burden: blood vs. Lymph node	8 children, age 1.1 - 10.6 years	ZDV+ddI+ NVP for 12 weeks	No safety data provided.
Mirochnick, M. et al (PACTG 250), completed	Safety and pk in maternal-fetal transmission	17 mother/infant pairs	a single dose of 200 mg NVP to mothers; placebo/single 2 mg/kg to newborns. All mothers/infants received 076 regimen of ZDV.	"No lab or clinical toxicity were noted. No rashes of any severity were noted."
Musoke, P. et al (Uganda), completed	Safety and pk in maternal-fetal transmission	21 mother/infant pairs	same to the above, except no 076 regimen was prescribed.	"No incidence of Steven-Johnson syndrome." "No serious episodes of fatigue, headache, nausea, fever, skin rash." "No abnormal lab data."
Korenbum-Kracer, A. et al.(PACTG 316), ongoing	Phase 3 maternal/fetal transmission study	Target: 1244 mother/infant pairs	single dose of NVP to mothers pretreated with various	No safety data available yet.

			combination regimens	
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Although the numbers are small, both ACTG 250 and the Uganda study showed that a single maternal dose of NVP given in labor with/without a single dose of NVP (2mg/kg) to the infant at 72 hours of life is safe and well tolerated in both mothers and infants.

As of August of 1998, ACTG 316 has enrolled 300 mother-newborn pairs into the trial. The study is expected to recruit patients outside the U.S. (Europe, South Africa) for speeding up recruitment.

Comment: Although results of ACTG 250 have been published, the applicant has not been able to access the dataset. Both the FDA and applicant have agreed that the pk analysis from this study should provide valuable pk information to neonates. Negotiation between the applicant and DAIDS is ongoing.

7 Spontaneous Adverse Event Reports in Children

7.1 From BIPI database

As of 06/25/98, BIPI has received 17 spontaneous reports of adverse events in children who have received marketed NVP. All these reports came from children in the US. Two cases of SJS were reported for two teenagers (each 16 years of age). The adverse events reported were similar to those seen in adults.

7.2 From FDA Adverse Event Reporting System (AERS)

As of 07/29/98, FDA has received 6 adverse event reports in children who have received marketed NVP. All but one were also included in the above database. The one exception was a case of SJS reported for a 9-year old boy from Florida, U.S. Of note that the reports for these three cases of SJS (including the 2 cases cited under 5.4.3.1) are clustered from Florida, possibly made by one reporter.

8. Reviewer's Summary and Conclusions

The applicant submitted in this supplement the results from 4 pediatric trials of NVP: Trials 1100.882 (ACTG 180), 1100.892 (Extension of 1100.882), 1100.1032 (ACTG 245), and 1100.859 (expanded access).

Based on FDA's review, Trial 1100.882 is deemed adequate in support of the recommended dosing regimen and safety use of NVP in pediatric patients. Results from study 1100.1032 and study 1100.892 were deemed supportive. Results from study 1100.859 were felt non-contributory to this supplement due to poor quality of the data collection.

Trial 1100.882 was an open-label, uncontrolled study of NVP as monotherapy, double therapy or triple therapy in 37 HIV-1 infected pediatric patients with a mean age of 3.3 years (range: 0.1 to 15 years) who were treated for a mean duration of 7.08 months.

Both formulations of NVP were used in the trial with a majority of patients receiving the oral suspension (89%).

Nevirapine was shown to be safe and well tolerated in Trial 1100.882. The most common drug related adverse events were similar to those seen in adults trials of NVP. About 16% of patients had rashes that were considered by the investigator to be related to NVP, which is identical to the incidence of NVP-attributable rash documented in placebo-controlled clinical trials in adults. No patients experienced severe rash and only one patient discontinued the trial due to rash. However, in Trial 1100.1032 two cases of SJS or SJS/TEN were documented.

Although the virological or immunological measures were only performed for a small number of patients in Trial 1100.882, activity of NVP was demonstrated with all of the NVP regimens (mono-, double and triple therapies). However sustained antiviral effects as measured by HIV-RNA was only shown in patients receiving triple therapy (NVP/ZDV/ddI).

Because of the small sample size, some observations made from Trial 1100.882 can only be considered as preliminary and thus need further investigations. Examples are, the efficacy of a triple therapy regimen (NVP/ZDV/ddI) as measured by surrogate markers in children, the appropriateness of a 2-week lead-in dosing regimen as judged by the incidence of rash events, the characteristics of rash occurrence in children including the onset and accompanied symptoms and signs (e.g. allergic reactions) and the incidence of hepatic adverse events. It is hopeful that these issues could be better delineated when results of Trial 1100.1032 would be fully analyzed.

The recommended dose is 4 mg/kg once daily for 2-week lead-in dosing for all pediatric patients, followed by 7 mg/kg b.i.d. for children below 8 years of age, or 4 mg/kg b.i.d. for children 8 years and older. In addition to the shortened lead-in period as previously discussed, two minor caveats should be noted:

- A cutoff age of 9 years (not 8 years) was used for both trials 1100.882 and 1100.1032.
- A dose of 150 mg/m² or 120 mg/m² based on body surface (not 7 mg/kg or 4 mg/kg) was used for both trials 1100.882 and 1100.1032.

Although the applicant has chosen a dose different than what had been used in trial 1100.882, the difference is deemed minor and can be justified by the population pk analysis of trial 1100.882 (please refer to Dr. Sekar's review for discussion.) Although a dose derived from body weight is more readily obtained than a dose derived from body surface area, the pk analysis suggests that either approach could be used in pediatric patients to mimic the NVP average concentration in adults taking 200 mg b.i.d.

In summary, the applicant's dosing recommendation is deemed acceptable.

Nevirapine has several properties which make it a potential candidate antiretroviral therapy to interrupt HIV-1 transmission in the intrapartum and early post-partum period.

The pharmacokinetic profile suggested that NVP would be rapidly absorbed and transferred to the infant *in utero* when given during labor and delivery. In addition, NVP has a long half-life of 25-30 hours which allows for a single dose of NVP administration to women in labor and a single oral dose of NVP administered to their infants. One such study design has been incorporated into trial ACTG 316 which is presently enrolling patients in the U.S., Europe and South Africa.

In conclusion, results of Trial 1100.882 have demonstrated the safety and tolerability of NVP given in children with HIV-1 infection. With the availability of the suspension formulation, NVP is deemed a useful addition to the pediatric antiretroviral therapeutic armamentarium and should be made available to physicians for treatment of children with HIV-1 infection.

9. Recommendation

Supplement 009 is recommended approvable.

**APPEARS THIS WAY
ON ORIGINAL**

Medical Officer

Teresa C. Wu, M.D., Ph.D.

Concurrences:

ATL/Maldonado
Div Dir/Jolson

CC:
Orig NDA
MO/WuT
MO/Haverkos
Biopharm
Chem/Lunn
PM/Kelly

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

DATE: September 4, 1998
FROM: Teresa Wu
SUBJECT: DSI request
TO: NDA 20-636/SE1 and NDA 20-933

ACTG 180 was a phase I/II pharmacokinetics, safety and activity study of VIRAMUNE in children. A total of 37 patients were recruited by 6 study sites. Because of the small number of patients enrolled in each study site, a scientific investigation was not requested.


Teresa Wu, MO
HFD-530

APPEARS THIS WAY
ON ORIGINAL

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

March 22, 1998 to June 21, 1998

The following section summarizes adverse event reports received during the reporting period of March 22, 1998 to June 21, 1998.

SERIOUS, UNEXPECTED ADVERSE EVENTS

During this period, there were 33 initial and 17 follow-up reports for VIRAMUNE® Tablets that met the criteria for 15-Day submission. See Section III. A., III. B.

SERIOUS, EXPECTED and NONSERIOUS ADVERSE EVENTS

During this period there were 10 serious expected reports, with 13 reported events: Stevens Johnson Syndrome (5), Rash (1), Rash Maculo-Papular (1), Pruritus (1), Hepatitis (2), Hepatic Function Abnormal (1), Bilirubinaemia (1) and Fever (1), and 76 nonserious adverse events reported in 39 patients.

Of the 76 initial nonserious adverse events, there were 19 cases coded as rash, including 1 report of Stevens-Johnson Syndrome, 10 cases coded as pruritus, 9 cases coded as fever, 2 cases coded as drug withdrawal and 6 cases coded in the Liver and Biliary System Disorder (Hepatic Function Abnormal (3), Jaundice (1), Bilirubinaemia (1) and Gamma GT Increased (1).

There was one follow-up serious expected event reported. This report was a case of Stevens Johnson Syndrome. There were five follow-up nonserious events reported in three patients.

CLINICAL SUMMARY

OVERVIEW OF THE REPORTING PERIOD

Thirty-three initial and seventeen follow-up reports containing at least one serious, unexpected event were submitted to the FDA during this review cycle.

Hepatic Toxicity

During this reporting period there has been no change in the pattern of events reported compared to what has already been observed with marketed VIRAMUNE®. The VIRAMUNE® label was revised to incorporate language regarding the potential hepatotoxicity associated with the use of VIRAMUNE®. The label change became effective May 20, 1998.

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

Skin Toxicity

Events within the skin and appendages body system continue to constitute the most commonly reported adverse events during this review cycle. The cases demonstrate a spectrum of skin reactions ranging from isolated rashes to hypersensitivity reactions which include rashes associated with constitutional symptoms such as fever, lymphadenopathy and pruritus, as well as organ toxicities involving the bone marrow, the kidneys and the liver. During this reporting period, two initial cases of epidermal necrolysis, along with follow-up information from two previously reported cases of epidermal necrolysis were forwarded to the agency. In addition, there were two initial reports of Stevens Johnson Syndrome reported. A VIRAMUNE® label change, effective May 20, 1998, incorporated language about the possibility of severe and life-threatening skin reactions associated with the use of VIRAMUNE®.

Pancreatitis

In this reporting period, there was one report of pancreatitis in association with use of marketed VIRAMUNE®. Didanosine was a suspect drug along with nevirapine. To date, the reports of pancreatitis appear to be isolated and more likely associated with use of concomitant drugs. Therefore, pancreatic toxicity specifically attributable to VIRAMUNE® seems unlikely.

Renal Failure

There continue to be rare reports of renal failure in association with use of marketed VIRAMUNE®. There is either too little information to make a clinical determination of the etiology of the event or there are other significant medical factors that are much more likely than VIRAMUNE® to be the cause of the event.

Drug Withdrawal

Since VIRAMUNE® has been marketed, there have been 20 non-serious reports suggesting diminished methadone levels during concurrent use with VIRAMUNE®. Two of the twenty reports occurred during this review cycle. As with the previous reports, limited clinical information was available in both cases. This interaction will be incorporated into the current VIRAMUNE® label as part of changes being effected supplement to the NDA.

Conclusion:

Except as noted above in the aforementioned subsections, during the current reporting period, there have been no reports, either individually or collectively, that have raised either new concerns or added new information to the current prescribing information for VIRAMUNE® Tablets.

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

Below are brief comments on serious, unexpected events of clinical importance from the individual reports:

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-000671	26MAR1998	INITIAL	ASTHENIA	36	YR M
	09JUN1998	FOLLOW-UP	HEPATITIS		

A 36 YEAR OLD FEMALE PATIENT IN FRANCE IN AN EXPANDED ACCESS TRIAL BEGAN VIRAMUNE, DIDANOSINE AND NELFINAVIR ON 01DEC97. THE PATIENT HAS A PREVIOUS MEDICAL HISTORY OF HEPATITIS B. ON 02JAN98 THE PATIENT'S SGOT WAS 19 U/L, AND SGPT WAS 19 U/L. ON 02FEB98 THE PATIENT PRESENTED WITH A HEPATIC CYTOLYSIS WITH ASTHENIA. VIRAMUNE WAS DISCONTINUED ON 06MAR98. LABORATORY RESULTS ON 02FEB98 REVEALED AN SGOT OF 176 U/L AND AN SGPT OF 382. ON 02MAR98 HER SGOT WAS 440 U/L AND SGPT WAS 1121 U/L. IT IS THE REPORTER'S JUDGEMENT THAT THE EVENT WAS CONSIDERED SERIOUS. THREE WEEKS AFTER VIRAMUNE WAS DISCONTINUED, THE HEPATIC ENZYMES WERE STILL RAISED. THERE WAS A REACTIVATION OF HEPATITIS B (WITH HVB'S ADN+). EPIVIR AND HYDREA WERE INTRODUCED. ON 30APR98, THE PATIENT'S SGOT AND SGPT WERE NORMAL. THE INVESTIGATOR AND CLINICAL MONITOR FELT THERE WAS NO REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY VIRAMUNE.

1998-000685	27MAR1998	INITIAL	EPIDERMAL NECROLYSIS	50	YR M
	29MAY1998	FOLLOW-UP			

A 50 YEAR OLD MALE PATIENT IN FRANCE IN AN EXPANDED ACCESS VIRAMUNE TRIAL BEGAN TRIAL DRUG 10FEB98 AT 200 MG A DAY. THIS THERAPY WAS COMBINED WITH NELFINAVIR (DOSING UNKNOWN) STARTED ON 10OCT97 AND DIDANOSINE (400 MG/DAY) STARTED ON 10FEB97. CONCOMITANT MEDICATION INCLUDES POSCAVIR (7 G/WEEK) STARTED ON 10FEB98, CYMEVAN (320 MG/WEEK) STARTED ON 10FEB98, AND BACTRIM (400 MG/DAY) STARTED ON 24FEB97. TWELVE DAYS AFTER THE ONSET OF TREATMENT WITH VIRAMUNE, THE PATIENT PRESENTED WITH A GENERALIZED RASH AND DRY EYES. TWO DAYS LATER, HE DEVELOPED A GENERALIZED CUTANEOUS ERUPTION WITH BULLAE ON LIPS, HANDS, FEET, PENIS, TRUNK AND AROUND HIS CATHETER HOLDER. THE PATIENT WAS DIAGNOSED WITH LYELL SYNDROME. THE EVENT WAS REPORTED TO BE IMMEDIATELY LIFE-THREATENING. WHEN THE EVENT OCCURRED, THE PATIENT WAS ALREADY IN A CONVALESCENCE HOME AND WAS NOT ADMITTED TO A HOSPITAL. HE WAS TREATED WITH CLARITYNE AND SOLUMEDROL. VIRAMUNE WAS DISCONTINUED ON 24FEB98. CONCOMITANT MEDICATIONS WERE CONTINUED. THE PATIENT RECOVERED WITHOUT SEQUELAE. THE INVESTIGATOR AND THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENT WAS CAUSED BY THE TRIAL DRUG.

1998-000708	27MAR1998	INITIAL	RASH MACULO-PAPULAR VERTIGO FEVER BACK PAIN HEADACHE	31	YR M
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A 31 YEAR OLD MALE PATIENT IN FRANCE IN A COMPASSIONATE USE TRIAL BEGAN VIRAMUNE (200 MG), ZIDOVUDINE, AND STAVUDINE ON 24FEB98. ON 03MAR98 THE PATIENT EXPERIENCED LUMBAR PAIN AND HEADACHES. ON 04MAR98 THE PATIENT DEVELOPED A FEVER, VERTIGO, MACULOPAPULAR RASH (ON HIS BACK). THE PATIENT WAS ADMITTED TO THE HOSPITAL AND VIRAMUNE WAS DISCONTINUED ON 04MAR98. THE INVESTIGATOR AND CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY THE TRIAL DRUG.

1998-000771	13APR1998	INITIAL	RETINAL DISORDER VISION ABNORMAL SCOTOMA CONJUNCTIVITIS	49	YR M
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SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

A 49 YEAR OLD MALE REPORTED THAT HE BEGAN TREATMENT WITH VIRAMUNE TABLETS FOR HIV-1 INFECTION DURING JAN97. IN JAN98 HE DEVELOPED BLURRED VISION. UPON FURTHER EXAMINATION, HE WAS FOUND TO HAVE "INFLAMMATION IN THE MEMBRANES OF THE EYE, AND CRYSTALS IN THE RETINA." THE PATIENT'S

MANUFACTURER	SUBMIT	SUBMIT			
CONTROL NUMBER	DATE	TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-000771	cont'd				

PHYSICIAN REPORTED THE EVENT AS DECREASED VISUAL ACQUITY, CENTRAL SCOTOMA, ACQUIRED COLOR VISUAL DEFECT WITH MACULAR PIGMENTARY CHANGES, CENTRAL MACULAR PIGMENT LOSS, AND DECREASED AMPLITUDE CONE CELL. ELECTRORETINOGRAM SHOWED EYE MACULOPATHY. THE PATIENT DISCONTINUED VIRAMUNE ON 17MAR98. THE PATIENT IS NOW IMPROVING AFTER ONE WEEK OFF VIRAMUNE.

1998-000792	06APR1998	INITIAL	STEVENS JOHNSON SYNDROME CREATINE PHOSPHOKINASE INCREASED	41	YR F
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A PHYSICIAN REPORTED THAT A 41 YEAR OLD FEMALE PATIENT BEGAN THERAPY WITH VIRAMUNE TABLETS, DOSING 200 MG DAILY, ON 26FEB98. ADDITIONAL DAILY ANTIRETROVIRAL THERAPY INCLUDED 2.25 MG OF ZALCITABINE, STARTED ON 26FEB98 AND 80 MG OF STAVUDINE, STARTED IN 1997. THE PATIENT TOLERATED 200 MG DOSING WITHOUT PROBLEMS (NO RASH). ON 12MAR98 VIRAMUNE DOSE WAS INCREASED TO 400 MG DAILY. ON 18MAR98 THE PATIENT DEVELOPED A RASH. SHE WENT TO THE EMERGENCY DEPARTMENT THAT SAME DAY AND VIRAMUNE WAS DISCONTINUED. LABORATORY VALUES REVEALED A CREATINE PHOSPHOKINASE (CPK) OF 65 UNITS/LITER (U/L), ASPARTATE TRANSAMINASE (AST) OF 37 U/L, ALANINE TRANSAMINASE (ALT) OF 45 U/L AND AN ALKALINE PHOSPHATASE OF 123 U/L. THE PATIENT WAS HOSPITALIZED AND ADMITTED TO THE INTENSIVE CARE UNIT. ON 19MAR98 THE RASH WAS DESCRIBED AS MACULOPAPULAR AND PRURITIC, WHICH PROGRESSED TO A FULL-BODY BLISTERING RASH ON 20MAR98. THE PATIENT WAS DIAGNOSED WITH STEVENS JOHNSON SYNDROME. NO SLOUGHING IS PRESENT. ANGIOEDEMA IS SIGNIFICANT IN THE FACIAL AREA. THE PHYSICIAN DESCRIBED THE PATIENT'S THROAT AS "ERODED", WITH NO RESPIRATORY COMPROMISE, HOWEVER SHE HAS HAD CONTINUAL COUGHING. SINCE 19MAR98 THE PATIENT HAS HAD EXCESSIVE DIARRHEA. HER EYES ARE NOTED TO BE REDDENED WITH SIGNIFICANT INFLAMMATION AND POSSIBLE CONJUNCTIVITIS. AN OCULAR EXAM HAS BEEN ORDERED. THE PATIENT'S VAGINAL AREA IS COVERED WITH VESICLES/BLISTERS AND HER VAGINAL AREA IS ALSO "ERODED". HER TEMPERATURE IS 104 DEGREES FAHRENHEIT (20MAR98). SHE IS BEING TREATED WITH FLUIDS AND 20 MG OF INTRAVENOUS SOLUMEDROL EVERY 8 HOURS. ON 20MAR98 LABORATORY VALUES REVEALED A CPK OF 1,119 U/L, AST OF 63 U/L, ALT OF 44 U/L AND ALK-P. OF 84 U/L. THE PATIENT'S CD4 COUNT AND VIRAL LEVEL ARE UNKNOWN. AS OF 26MAR98 IT WAS REPORTED THAT THE PATIENT IS NOW IN A BURN UNIT. THE PATIENT'S OTHER MEDICATIONS ARE BACTRIM AND ZANTAC (BOTH STARTED IN 1997). ALL CONCOMITANT MEDICATIONS WERE CONTINUED. CONCOMITANT DISEASES WERE NOT REPORTED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

1998-000809	02APR1998	INITIAL	BACK PAIN	30	YR F
	27APR1998	FOLLOW-UP	RENAL PAIN ABDOMINAL PAIN VOMITING NAUSEA		

A 30 YEAR OLD FEMALE IN FRANCE IN AN EXPANDED ACCESS TRIAL BEGAN VIRAMUNE TABLETS ON 21OCT97 WITH CURRENT DOSING OF 400 MG DAILY. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES ABACAVIR AND ZIDOVUDINE, ALSO STARTED IN OCT97. ON 02MAR98 THE PATIENT WAS HOSPITALIZED FOR ABDOMINAL PAINS, LEFT LUMBAR FOSSA PAINS, NAUSEA AND VOMITING. ABDOMINAL RADIOGRAPHY WAS NEGATIVE. RENAL ECHOGRAPHY REVEALED A DILATATION OF THE PYLEO CALICEAL CAVITIES IN THE LEFT KIDNEY. THE PATIENT WAS DIAGNOSED WITH RENAL COLIC AFTER SPONTANEOUSLY EXPELLING A URINARY CALCULUS. SHE WAS TREATED WITH A COMBINATION OF PHLOROGLUCINOL / TRIMETHYLPHLOROGLUCINOL (SPASFON/SPASFON-LYOC) AND RECOVERED ON 07MAR98. ON 12MAR98 LABORATORY TESTS REVEALED THE PRESENCE OF CALCIUM PHOSPHATE AND CALCIUM OXALATE CRYSTALS. VIRAMUNE, ZIDOVUDINE AND ABACAVIR WERE CONTINUED. THE INVESTIGATOR JUDGED A REASONABLE POSSIBILITY THE EVENTS WERE RELATED; "FOR THE PHYSICIAN, THE CAUSAL RELATIONSHIP BETWEEN VIRAMUNE, ABACAVIR AND THIS LITHIASIS COULD NOT BE EXCLUDED".

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

THE CLINICAL MONITOR JUDGED A REASONABLE POSSIBILITY THAT THE EVENTS ABDOMINAL PAIN, LUMBAR PAIN, NAUSEA AND VOMITING WERE RELATED TO VIRAMUNE BUT JUDGED THE EVENT RENAL COLIC NOT RELATED TO VIRAMUNE.

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-000819	09APR1998 27APR1998	INITIAL FOLLOW-UP	RASH ERYTHEMATOUS FEVER PANCYTOPENIA PNEUMONITIS RESPIRATORY DISORDER COUGHING DYSURIA	41	YR M

A 41 YEAR OLD MALE PATIENT IN FRANCE, WITH A MEDICAL HISTORY OF PSORIASIS AND TOXICOMANIA, ENTERED INTO AN EXPANDED ACCESS VIRAMUNE TRIAL, COMBINED WITH STAVUDINE, NELFINAVIR (2250 MG/DAY) AND DIDANOSINE. ON 14FEB98 THE PATIENT EXPERIENCED ERYTHRODERMIA (GENERALIZED DESQUAMATION WITH NEITHER BULLA NOR MUCOUS LESION), MUCOPURULENT SPUTUM (NORMAL THORACIC X-RAY), COUGHING, RALES, FEVER AND MICTURITION BURNS. THE PATIENT WAS HOSPITALIZED ON 17FEB98 AND VIRAMUNE WAS DISCONTINUED. DURING THE PATIENT'S HOSPITAL STAY A PANCYTOPENIA WAS NOTICED. THE PATIENT RECOVERED AND WAS DISCHARGED ON 25FEB98. THE DERMATOLOGIST FELT THAT THE EVENTS WERE RELATED TO EITHER PSORIASIS OR VIRAMUNE TOXIDERMA. THE INVESTIGATOR FELT THERE WAS A REASONABLE POSSIBILITY THAT ALL THE EVENTS WERE CAUSED BY VIRAMUNE, WHILE THE CLINICAL MONITOR FELT ONLY THE ERYTHRODERMA AND FEBRILE SYNDROME WERE CAUSED BY VIRAMUNE.

1998-000853	09APR1998	INITIAL	STEVENS JOHNSON SYNDROME HERPES ZOSTER CYTOMEGALOVIRUS INFECTION	48	YR M
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A 48 YEAR OLD MALE PATIENT IN FRANCE IN A CLINICAL TRIAL FROM GLAXO WELLCOME BEGAN TREATMENT WITH 1592U89 300 MG TWICE DAILY AND VIRAMUNE ON 10DEC97. THE PATIENT HAD A HISTORY OF CHILDHOOD LABIAL HERPES. CO-TRIMOXAZOLE AND AZITHROMYCIN WERE TAKEN CONCURRENTLY. APPROXIMATELY ONE MONTH AFTER THE START OF THE STUDY MEDICATIONS THE PATIENT DEVELOPED MODERATE ORAL ULCERATION AND WAS HOSPITALIZED. HE ALSO PRESENTED WITH PAPULAR LESIONS ON HIS TRUNK, RED EYES, FEVER (37.7 C), HERPES, CYTOMEGALOVIRUS AND TOXIDERMIA. THE STUDY MEDICATIONS WERE TEMPORARILY INTERRUPTED ALONG WITH OTHER ANTIVIRAL CONCURRENT MEDICATION. THE PATIENT COMMENCED TREATMENT WITH AN INTRAVENOUS INFUSION OF ACYCLOVIR AND APPROXIMATELY ELEVEN DAYS LATER THE EVENT HAD RESOLVED. THE PATIENT WAS RECHALLENGED WITH 1592U89 AND AN INCREASED DOSE OF VIRAMUNE AFTER TEN DAYS. TWO DAYS AFTER THIS RECHALLENGE THE PATIENT DEVELOPED AN OUTBREAK OF LESIONS AROUND HIS MOUTH AND RED EYES. ACYCLOVIR WAS RECOMMENCED. APPROXIMATELY THREE DAYS AFTER THE RECHALLENGE AND TWO MONTHS AFTER THE INITIAL START OF THE STUDY MEDICATIONS, THE PATIENT DEVELOPED SEVERE CONJUNCTIVITIS, SEVERE ERYTHEMA ON THE SOLES OF HIS FEET AND PALMS OF HIS HANDS, MODERATE SUPERFICIAL MOUTH ULCERATION AND OEDEMA OF HIS EYELIDS. THERE WAS NO FEVER NOTED OR ANY DIGESTIVE PROBLEMS AND HEPATIC ASSESSMENTS WERE NORMAL. THE INVESTIGATOR DIAGNOSED STEVENS JOHNSON SYNDROME AND PERMANENTLY DISCONTINUED THE 1592U89 AND THE VIRAMUNE. THE EVENT RESOLVED AFTER APPROXIMATELY TWO MONTHS. THE INVESTIGATOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE RELATED TO THE 1592U89 AND THE VIRAMUNE.

1998-000861	08APR1998	INITIAL	PAIN OEDEMA HEADACHE DYSPNOEA ASTHENIA FEVER RASH MACULO-PAPULAR		YR F
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SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

A SOCIAL WORKER REPORTED THAT A FEMALE PATIENT WITH AIDS WHO HAS BEEN TREATED WITH VIRAMUNE TABLETS SINCE APPROXIMATELY 09MAR98 DEVELOPED A RASH, HEADACHE, SWOLLEN EYES, AND DIFFICULTY BREATHING. WHEN SEEN AT THE HOSPITAL THE PATIENT HAD SHORTNESS OF BREATH WITH AN INCREASED EXPIRATORY PHASE. SHE WAS GIVEN ALBUTEROL AND THESE SYMPTOMS RESOLVED. THE PATIENT HAS ALSO

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MANUFACTURER	SUBMIT	SUBMIT			
CONTROL NUMBER	DATE	TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX

1998-000861 cont'd

BEEN WEAK WITH ACHEs AND A FEVER OF 100.0 F (ORAL). THE RASH IS DESCRIBED AS FULL BODY DIFFUSE, ERYTHEMATOUS, MACULOPAPULAR WITH PAPULES ON HER BACK AND RIGHT ARM. THE PATIENT ALSO HAS SIGNIFICANT FACIAL SWELLING. NO MUCOUS MEMBRANES ARE INVOLVED. THE PATIENT WAS TREATED WITH BENADRYL (25 MG) AND SOLUMEDROL (120 MG). THE PATIENT WAS ADMITTED TO THE HOSPITAL AND DIAGNOSED WITH MACULO-PAPULAR RASH. ALL SYMPTOMS RESOLVED AND THE PATIENT WAS DISCHARGED ON 27MAR98

1998-000888	08APR1998	INITIAL	FEVER	42	YR M
	27APR1998	FOLLOW-UP	HEADACHE HEPATITIS CHOLESTATIC ABDOMINAL PAIN VOMITING DIARRHOEA STUPOR		

A 42 YEAR OLD MALE PATIENT IN FRANCE IN AN EXPANDED ACCESS VIRAMUNE CLINICAL TRIAL BEGAN VIRAMUNE THERAPY ON 31OCT97. VIRAMUNE TREATMENT WAS COMBINED WITH ABACAVIR, RITONAVIR AND SAQUINAVIR. THE PATIENT HAS A MEDICAL HISTORY OF HEPATITIS B. THE PATIENT DOUBLED THE NORMAL DOSE OF VIRAMUNE, FOR THE FIRST 14 DAYS HE TOOK 2 TABLETS PER DAY, THEN 4 TABLETS PER DAY UNTIL 15DEC97 WHEN THE DOSE WAS CORRECTED TO 2 TABLETS PER DAY. ON 31OCT97 THE PATIENT EXPERIENCED CHOLESTASIS, AND ON 14NOV97 HE EXPERIENCED A LOSS OF CONSCIOUSNESS. HE HAS EXPERIENCED FEVER, VOMITING, DIARRHEA, ABDOMINAL PAINS AND HEADACHES SINCE 24NOV97. THE PATIENT WAS HOSPITALIZED FROM 01DEC97 TO 05DEC97 FOR AGGRAVATION OF DIARRHEA AND CHOLESTASIS. THE PATIENT NOTED HE HAD BEEN SUFFERING FROM INTERMITTENT DIARRHEA FOR ONE YEAR. VIRAMUNE WAS CONTINUED. THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY ALL THE EVENTS EXCEPT THE LOSS OF CONSCIOUSNESS WERE CAUSED BY THE VIRAMUNE.

1998-000930	09APR1998	INITIAL	BILIRUBINAEMIA INFLUENZA-LIKE SYMPTOMS PANCYTOPENIA HEPATIC FUNCTION ABNORMAL	54	YR M
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A PHARMACIST REPORTED THAT A 54 YEAR OLD BLACK MALE WITH AIDS WHO HAD BEEN TAKING VIRAMUNE SINCE NOVEMBER 1997 DEVELOPED A FLU-LIKE ILLNESS IN LATE FEBRUARY 1998 WHICH INCLUDED: FEVER, CHILLS, HEADACHE, DIARRHEA AND COUGH. THESE SYMPTOMS LASTED FOR THREE WEEKS. ON 24MAR98 THE PATIENT DEVELOPED PANCYTOPENIA (HCT 13 ON 24MAR98), DOWN FROM 33 IN JANUARY 1998, PLATELETS 66 ON 24MAR98, DOWN FROM 78 IN JANUARY 1998, AND WHITE BLOOD CELLS 1.7 ON 24MAR98, DOWN FORM 2.1 IN JANUARY 1998. THE PATIENT'S SGOT AND SGPT WERE ALSO ELEVATED FROM BASELINE (SGOT 327, SGPT 281) AND HIS TOTAL BILIRUBIN WAS ELEVATED TO 4.9 WITH A DIRECT BILIRUBIN OF 3.4. THE PATIENT WAS HOSPITALIZED ON 24MAR98 FOR EVALUATION AND TREATMENT. THE PATIENT RECEIVED 2 UNITS OF PACKED RED BLOOD CELLS SHORTLY AFTER ADMISSION. THE PATIENT'S WORK-UP INCLUDED A VIRAL CULTURE FOR PARVOVIRUS THE RESULTS OF WHICH ARE STILL PENDING. HAPTOGLOBIN 24 (WITHIN NORMAL RANGE). NO RASH WAS REPORTED PRIOR TO OR DURING THE HOSPITALIZATION. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-000992	13MAY1998	INITIAL	HERPES SIMPLEX	42	YR M

A 42 YEAR OLD WHITE MALE REPORTED THAT HE BEGAN THERAPY WITH VIRAMUNE ON 12MAR98. ON 08APR98 HE DEVELOPED A RASH DESCRIBED AS RED SPOTS, SOME WITH FLUID, ALL OVER HIS BODY. THE PATIENT STATES HE WAS TAKING BENADRYL AS TREATMENT FOR THE RASH, BUT THAT THE RASH HAS NOT IMPROVED. ON 04APR98, HE ALSO EXPERIENCED A THROAT ACHE AND ABDOMINAL PAIN; AS FRIENDS OF HIS ARE EXPERIENCING COLDS WITH GASTROINTESTINAL UPSET, HE DOES NOT FEEL THESE SYMPTOMS ARE RELATED TO THE RASH. ON 29APR98 ADDITIONAL INFORMATION WAS RECEIVED FROM THE PATIENT'S PHYSICIAN INDICATING THAT THE PATIENT WAS HOSPITALIZED FOR A RASH ON HIS CHEST, FACE, LIPS AND ARMS. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES VIRACEPT FOR SIX MONTHS AND STAVUDINE SINCE 12MAR98. NORVIR WAS STARTED ON 09APR98. VIRAMUNE WAS DISCONTINUED ON 13APR98. THE PATIENT WAS FOUND TO HAVE HERPES AND WAS TREATED WITH ZOVIRAX. HE RECOVERED ON 18APR98.

1998-001013	06MAY1998	INITIAL	PRURITUS RASH MACULO-PAPULAR OEDEMA PERIORBITAL	49	YR M
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A 49 YEAR OLD MALE PATIENT IN FRANCE IN AN EXPANDED ACCESS VIRAMUNE TRIAL BEGAN VIRAMUNE TABLETS ON 25FEB98. VIRAMUNE DOSING AT THE TIME OF THE EVENT WAS 400 MG DAILY. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES VIRACEPT AND ABACAVIR SINCE 25FEB98. CONCOMITANT MEDICATIONS ARE PROZAC SINCE 25FEB98 AND ZYRTEC SINCE 21NOV97 THE PATIENT HAS A HISTORY OF DEPRESSION, ECZEMA AND DRUG ALLERGIES TO ASPIRIN, AUGMENTIN, CLAFORAN AND BACTRIM. ON 18MAR98 THE PATIENT DEVELOPED A RASH ON HIS FACE, SEVERE PRURITUS OF HIS EYES AND PERIORBITAL EDEMA. THE PATIENT WAS HOSPITALIZED AND TREATED WITH SOLUMEDROL AND POLARAMINE (CHLORPHENIRAMINE MALEATE). THE "ALLERGY" REPORTEDLY DECREASED WITHIN 24 HOURS BUT THE PATIENT HAS NOT YET RECOVERED. VIRAMUNE WAS DISCONTINUED ON 26MAR98. ABACAVIR AND THE OTHER CONCOMITANT MEDICATIONS WERE CONTINUED. THE INVESTIGATOR REPORTED A REASONABLE CAUSAL RELATIONSHIP BETWEEN THE EVENTS AND VIRAMUNE AND/OR ABACAVIR. THE CLINICAL MONITOR JUDGED THERE WAS A REASONABLE POSSIBILITY THAT THE EVENTS WERE RELATED TO VIRAMUNE.

1998-001027	02JUN1998	INITIAL	AVASCULAR NECROSIS FEMORAL HEAD	40	YR M
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A PHYSICIAN REPORTED THAT A 40 YEAR OLD WHITE MALE PATIENT BEGAN THERAPY WITH VIRAMUNE TABLETS, 200 MG DAILY, IN JUN96. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDED ZIDOVUDINE AND LAMIVUDINE TAKEN SINCE JAN96. BETWEEN JAN96 AND FEB96 THE PATIENT RECEIVED A 3 WEEK REGIMEN OF STEROID THERAPY, WITH TAPERING, FOR PCP PNEUMONIA. HE HAS NO OTHER HISTORY OF STEROID USE. IN NOV97 THE PATIENT DEVELOPED LEFT HIP PAIN. AT THAT TIME, AN X-RAY WAS NORMAL. THE PAIN PERSISTED. IN APR98 THE PAIN BECAME MORE SEVERE CAUSING THE PATIENT TO SEEK MEDICAL ATTENTION. HE HAD X-RAYS AND MRI'S OF BOTH HIP (DATES UNKNOWN) AND A RADIOLOGIST DIAGNOSED AVASCULAR NECROSIS OF THE LEFT FEMUR. THE PATIENT'S PHYSICIAN INDICATED THE EVENT WAS SEVERELY DISABLING. THE PATIENT HAS BEEN RECEIVING MEDICATION FOR PAIN CONTROL AND IS SCHEDULED FOR A TOTAL HIP ARTHROPLASTY IN JUN98. BACTRIM WAS REPORTED TO BE AN ALTERNATE SUSPECT DRUG AND WAS DISCONTINUED ON 13APR98. VIRAMUNE, 400 MG DAILY, WAS DISCONTINUED ON 14APR98. ZIDOVUDINE WAS REPORTED TO HAVE ALSO BEEN DISCONTINUED IN APR98. AT THIS TIME, STAVUDINE, DIDANOSINE, CRIXIVAN AND DAPSONE WERE STARTED.

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-001029	27APR1998	INITIAL	SARCOMA	26	YR M

A REPORT WAS RECEIVED FROM A PHYSICIAN IN SWITZERLAND CONCERNING A 26 YEAR OLD MALE PATIENT IN THE INTENSIVE CARE UNIT OF A HOSPITAL. THE PATIENT BEGAN TAKING VIRAMUNE TABLETS ON 20MAR98. RITONAVIR AND SAQUINAVIR WERE ALSO STARTED THE SAME DAY (20MAR98). TEN DAYS LATER ON 30MAR98 THE PATIENT DEVELOPED DYSPNEA. VIRAMUNE, RITONAVIR, AND SQUINAVIR WERE DISCONTINUED ON 31MAR98. AN AUTOPSY WAS PERFORMED, RESULTS ARE PENDING. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

1998-001050	27APR1998	INITIAL	ENANTHEMA ANGIOEDEMA RASH	26	YR M
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A 26 YEAR OLD MALE PATIENT IN FRANCE IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL BEGAN TREATMENT WITH VIRAMUNE COMBINED WITH STAVUDINE AND DIDANOSINE ON 13MAR98. ON 23MAR98 THE PATIENT BEGAN TAKING AMOXICILLIN FOR A SORE THROAT. ON 26MAR98 THE PATIENT PRESENTED WITH A GENERALIZED TOXIDERMIA WITH TWO BULLAE (ON EARS), ENANTHEMA AND QUINCKE'S EDEMA. THE AMOXICILLIN AND VIRAMUNE WERE DISCONTINUED. CORTICOTHERAPY WAS STARTED AND THE PATIENT RECOVERED ON 06APR98. THE INVESTIGATOR AND CLINICAL MONITOR FEEL THERE IS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY VIRAMUNE AND/OR AMOXICILLIN (FLEMOXINE).

1998-001064	21APR1998	INITIAL	SUICIDE ATTEMPT DEPRESSION	43	YR M
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A 43 YEAR OLD MALE PATIENT IN ENGLAND IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL WAS PRESCRIBED VIRAMUNE (400 MG/DAILY) STARTING ON 21AUG97. HE WAS ALSO TAKING ZIDOVUDINE (500 MG/DAILY) AND LAMIVUDINE (300 MG/DAILY). THE PATIENT DEVELOPED A SUDDEN ONSET OF DEPRESSION (DATE UNKNOWN), WHICH LED TO A PARASUICIDE ATTEMPT (DATE UNKNOWN) WITH AN OVERDOSE OF TEMAZEPAM WITH PRIOR ALCOHOL CONSUMPTION. VIRAMUNE WAS CONTINUED. THE PATIENT RECOVERED FROM THE SUICIDE ATTEMPT. THE OUTCOME OF THE DEPRESSION IS UNKNOWN AT THIS TIME. THE PATIENT HAS NO PRIOR HISTORY OF DEPRESSION OR PSYCHIATRIC ILLNESS. ZIDOVUDINE AND LAMIVUDINE WERE CONSIDERED ALTERNATE SUSPECT DRUGS. THE PATIENT WAS HOSPITALIZED AND TREATED WITH TRAZADONE AND SUPPORTIVE THERAPY. THE INVESTIGATOR AND CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE SUICIDE ATTEMPT WAS CAUSED BY THE TRIAL DRUG.

1998-001114	01MAY1998	INITIAL	RASH MACULO-PAPULAR	38	YR F
	29MAY1998	FOLLOW-UP	DYSAESTHESIA MYALGIA FEVER LYMPHADENOPATHY CERVICAL		

A 39 YEAR OLD FEMALE PATIENT IN FRANCE IN AN EXPANDED ACCESS TRIAL BEGAN VIRAMUNE TABLETS ON 17FEB98. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES ZIDOVUDINE AND LAMIVUDINE, BOTH STARTED ON 27MAY97. NO CONCOMITANT DISEASES WERE REPORTED: ON 06MAR98 THE PATIENT DEVELOPED A MACULAR ERYTHEMA ON HER TRUNK AND LIMBS, FEVER OF 39 DEGREES CENTIGRADE, BURNING SENSATIONS, MYALGIA AND CERVICAL ADENOPATHY. VIRAMUNE WAS DISCONTINUED ON 06MAR98. CETIRIZINE AND LYSINE ACETYLSALICYLATE WERE ADMINISTERED. THE EVENTS WERE REPORTED TO BE LIFE-THREATENING, HOWEVER, THE PATIENT WAS NOT HOSPITALIZED. THE PATIENT RECOVERED ON 11MAR98. THE INVESTIGATOR JUDGED THERE WAS A REASONABLE POSSIBILITY OF A RELATIONSHIP BETWEEN THE EVENTS AND VIRAMUNE. THE CLINICAL MONITOR JUDGED THERE WAS A REASONABLE POSSIBILITY OF A RELATIONSHIP BETWEEN VIRAMUNE AND ALL OF THE EVENTS EXCEPT CERVICAL ADENOPATHY

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-001168	06MAY1998	INITIAL	MENSTRUAL DISORDER MENORRHAGIA	32	YR F

A 32 YEAR OLD FEMALE PATIENT IN FRANCE IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL BEGAN VIRAMUNE THERAPY ON 17APR98 COMBINED WITH ZIDOVUDINE, LAMIVUDINE, AND PREDNISOLONE. ON 19APR98, THE PATIENT EXPERIENCED MENORRHAGIA AND METRORRHAGIA. SHE WAS HOSPITALIZED AND RECEIVED A TRANSFUSION. THE PATIENT HAS NOT YET RECOVERED. THE INVESTIGATOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY THE TRIAL DRUG, WHILE THE CLINICAL MONITOR FELT THERE WAS NO REASONABLE POSSIBILITY THEY WERE CAUSED BY THE TRIAL DRUG.

1998-001170	07MAY1998	INITIAL	OEDEMA	39	YR F
	05JUN1998	FOLLOW-UP	ARTHRALGIA RASH MACULO-PAPULAR MYALGIA PRURITUS INFLUENZA-LIKE SYMPTOMS		

A 39 YEAR OLD FEMALE PATIENT IN FRANCE IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL BEGAN VIRAMUNE THERAPY COMBINED WITH ZIDOVUDINE AND DIDANOSINE ON 04APR98. ON 10APR98, THE PATIENT EXPERIENCED AN INFLUENZA-LIKE SYNDROME (FEVER, HEADACHE, AND COUGH). ON 14APR98, SHE DEVELOPED A MORBILLIFORM RASH, MYALGIA AND ARTHRALGIA. ON 16APR98, THE RASH INCREASED WITHOUT UNSTICKING AND FACIAL EDEMA DEVELOPED. ON THE FOLLOWING DAY (17APR98), THE RASH SPREAD BUT A PRURITUS APPEARED. VIRAMUNE WAS DISCONTINUED ON 14APR98. THE INVESTIGATOR AND CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY THE TRIAL DRUG.

1998-001195	12MAY1998	INITIAL	RASH ARTHRALGIA HEPATIC ENZYMES INCREASED FEVER	43	YR M
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A 43 YEAR OLD MALE PATIENT IN FRANCE IN AN OPEN-LABEL VIRAMUNE TABLETS CLINICAL TRIAL BEGAN TRIAL MEDICATION ON 07APR98. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES STAVUDINE (D4T) AND INDINAVIR SINCE 07APR98. NO OTHER CONCOMITANT MEDICATIONS OR DISEASES WERE REPORTED. ON 19APR98 THE PATIENT DEVELOPED A SEVERE GENERALIZED CUTANEOUS RASH (EXCLUDING FACE, HANDS AND FEET), FEVER, ARTHRALGIA AND ELEVATED LIVER ENZYMES; ALANINE TRANSAMINASE (ALAT) OF 209 UI/L AND ASPARTATE TRANSAMINASE (ASAT) OF 163 UI/L. THE EVENTS WERE CONSIDERED LIFE-THREATENING BECAUSE THE RASH WAS JUDGED GRADE IV AND THE ELEVATED LIVER ENZYMES WERE JUDGED GRADE III. VIRAMUNE WAS DISCONTINUED ON 21APR98 AND THE PATIENT WAS TREATED WITH AN ANTIHISTAMINE. THE PATIENT WAS NOT HOSPITALIZED. WHEN THE ANTIHISTAMINE WAS DISCONTINUED THE RASH REAPPEARED. AT THIS TIME, STAVUDINE AND INDINAVIR WERE DISCONTINUED (DATE NOT REPORTED). BOTH THE INVESTIGATOR AND THE CLINICAL MONITOR JUDGED THERE WAS A REASONABLE POSSIBILITY THAT THE EVENTS WERE RELATED TO THE TRIAL MEDICATION.

1998-001229	13MAY1998	INITIAL	ARTHRITIS FEVER PURPURA	72	YR M
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A 72 YEAR OLD MALE PATIENT IN FRANCE IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL BEGAN VIRAMUNE THERAPY COMBINED WITH NELFINAVIR AND DIDANOSINE ON 31MAR98. ON 16APR98 THE PATIENT EXPERIENCED VASCULAR PURPURA, POLYARTHRITIS AND FEVER AND WAS HOSPITALIZED. VIRAMUNE WAS DISCONTINUED ON 27APR98. THE INVESTIGATOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS -

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
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1998-001229 cont'd
WERE CAUSED BY VIRAMUNE, WHILE THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY -- THE VASCULAR PURPURA AND FEVER WERE CAUSED BY VIRAMUNE, AND NO REASONABLE POSSIBILITY THE POLYARTHRITIS WAS CAUSED BY VIRAMUNE.

1998-001287	20MAY1998	INITIAL	GALL BLADDER DISORDER ABDOMINAL PAIN NAUSEA HEPATIC FUNCTION ABNORMAL EOSINOPHILIA LEUKOCYTOSIS FEVER	38	YR M
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A PHYSICIAN REPORTED THAT A 38 YEAR OLD MALE, WHO IS NOT ANTIRETROVIRAL NAIVE, WITH A CD4 COUNT <100 CELLS/UL FOR MORE THAN 2 YEARS, HAD BEEN DOING WELL CLINICALLY AND VIROLOGICALLY ON INDINAVIR, STAVUDINE, LAMIVUDINE AND IN A BISPOM STUDY (DRUG VS PLACEBO); DEVELOPED A RISING VIRAL LOAD (NOT DRAMATIC) UP TO 12,000 COPIES. HE WAS SWITCHED TO VIRACEPT, DIDANOSINE, AND VIRAMUNE (PLUS BISPOM STUDY MEDICATION). FOUR DAYS AFTER ESCALATING TO BID VIRAMUNE HE DEVELOPED FEVER, ABDOMINAL PAIN AND NAUSEA. HE WENT TO THE EMERGENCY ROOM AND WAS FOUND TO HAVE AN ELEVATED WHITE BLOOD CELL COUNT (WBC) WITH A SHIFT TO THE LEFT, ELEVATED LIVER FUNCTION TESTS, INCLUDING TRANSAMINASES IN RANGE OF 6-8000 IU/L, DIRECT BILIRUBIN OF 4.5 MG/DL, ALKALINE PHOSPHATASE AND GAMMA-GLUTAMYL TRANSFERASE (GGT) ELEVATIONS. AN ULTRASOUND REVEALED A THICKENED GALLBLADDER WALL, NO STONES BUT SLUDGING AND DUCTS OF NORMAL SIZE. HE WAS TAKEN TO SURGERY FOR PRESUMPTIVE CHOLECYSTITIS, NO FRANK INFECTION WAS FOUND, BUT A LIVER LACERATION NECESSITATED A TRANSFUSION. AT THIS TIME, HE DEVELOPED A MARKED, ACUTE REACTION, IMMEDIATELY DEVELOPING HIVES/RASH AND HYPOTENSION WHICH REQUIRED FLUID SUPPORT AND EPINEPHRINE. THE GALLBLADDER (REMOVED PRIOR TO TRANSFUSION) SHOWED NO EVIDENCE OF INFECTION, BUT THE WALL WAS STUDDED WITH NODULES THAT SHOWED EOSINOPHILIC INFILTRATES. ONLY AFTER HIS MEDICATIONS WERE HELD DID THE PATIENT CLINICALLY BEGIN TO IMPROVE (REGARDING RASH, FEVERS, ELEVATED WBC AND LFT'S). THE DAY AFTER SURGERY, HIS PERIPHERAL SMEAR DEVELOPED A MARKED EOSINOPHILIA (>25%) THAT GRADUALLY RESOLVED. SINCE THEN, HIS PROPHYLACTIC MEDICATIONS AND A NEW REGIMEN WITH DIDANOSINE AND VIRACEPT HAVE BEEN WELL TOLERATED. ADDITIONAL INFORMATION HAS BEEN REQUESTED.

1998-001288	21MAY1998	INITIAL	EOSINOPHILIA HEPATIC FUNCTION ABNORMAL LEUKOCYTOSIS FEVER PNEUMONIA MALAISE CHOLECYSTITIS RASH		YR NR
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A PHYSICIAN REPORTED THAT A PATIENT ON AN UNSUCCESSFUL REGIMEN OF AZT, 3TC, AND D4T HAD A VIRAL LOAD OF 10000. THE PATIENT'S TREATMENT REGIMEN WAS CHANGED TO NELFINAVIR, DIDANOSINE, AND VIRAMUNE (START DATE UNKNOWN). ONE WEEK AFTER ESCALATING TO FULL DOSE OF VIRAMUNE (400 MG/DAY) THE PATIENT DEVELOPED A FEVER (104 F), MALAISE, ELEVATED TRANSAMINASE, AND RASH. THE PATIENT WAS HOSPITALIZED DUE TO THESE SYMPTOMS AND WORSENING LIVER FUNCTION TESTS (INCREASED BILIRUBIN, ALK PHOS, AND GGT). THE PATIENT'S WHITE BLOOD CELL COUNT IS ALSO MARKEDLY ELEVATED (22,000) WITH 20% BANDS. A CHEST X-RAY SHOWED POSSIBLE EARLY INFILTRATE AND AN ULTRASOUND SHOWED GALLBLADDER SLUDGE AND WALL THICKENING. MEDICATIONS WERE STOPPED AND THE PATIENT WAS TREATED FOR A POSSIBLE UNDERLYING PNEUMONIA. THE PATIENT IMPROVED CLINICALLY, THOUGH A LOW GRADE FEVER AND INCREASED WBC (12 - 14K RANGE WITH INCREASING EOSINOPHILS) STILL PERSIST. THE PATIENT RECOVERED ONE WEEK LATER ON ORAL AUGMENTIN. THREE DAYS LATER HE DEVELOPED A RASH AND LOW GRADE FEVER, WBC UP TO 26K AND 22 % EOSINOPHILS. AUGMENTIN WAS STOPPED AND PREDNISONE WAS STARTED. THE PATIENT DEVELOPED ABDOMINAL PAIN AND A WBC OF 60K WITHIN 24 HOURS. ALL MEDICATION

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-001409	03JUN1998	INITIAL	FEVER PALPITATION ARTHRALGIA	38 YR	M

A 38 YEAR OLD MALE PATIENT IN SWITZERLAND BEGAN THERAPY WITH VIRACEPT, VIRAMUNE, AND HIVID ON 15DEC97. THREE WEEKS AFTER STARTING THERAPY THE PATIENT DEVELOPED STRONG JOINT PAIN, PALPITATIONS, AND A FEVER. THE PATIENT REQUIRED HOSPITALIZATION (DATE UNKNOWN). AFTER ANTI-VIRAL THERAPY WAS DISCONTINUED (30APR98) THE JOINT PAIN AND PALPITATIONS RESOLVED. THE PATIENT'S FEVER (37.5 C) LASTED A MONTH AND A HALF.

1998-001437	08JUN1998	INITIAL	VOMITING PRURITUS RASH MACULO-PAPULAR FEVER	16 YR	M
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A 16 YEAR OLD MALE WITH CONGENITALLY ACQUIRED HIV IN AN INVESTIGATOR'S OWN BEGAN VIRAMUNE, NELFINAVIR AND STAVUDINE 200 MG A DAY ON 03MAR98. ON 10MAR98 THE PATIENT DEVELOPED AN ERYTHEMATOUS MACULAR PAPULAR PRURITIC RASH WITH NO FEVER, CONSTITUTIONAL SIGNS OR MUCOUS MEMBRANE INVOLVEMENT. HE WAS SEEN IN THE CLINIC ON THE MORNING OF 11MAR98 WITH A GRADE 2A TOXICITY. HE CONTINUED ALL TRIAL DRUGS AND STARTED BENADRYL (25 MG EVERY 4-6 HOURS) FOR PRURITUS. ON 12MAR98 THE PATIENT VOMITED 3 TIMES THEN HAD A FEVER OF 103.5 F. HE TOOK TYLENOL AND WAS ADMITTED TO THE HOSPITAL FOR OBSERVATION. HE HAD NO FURTHER FEVER, AND NO MUCOUS MEMBRANE INVOLVEMENT, CONSTITUTIONAL SIGNS OR LYMPHADENOPATHY. VIRAMUNE WAS DISCONTINUED 12MAR98. THE INVESTIGATOR AND THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY THE TRIAL DRUG.

1998-001491	09JUN1998	INITIAL	RIGORS FEVER	38 YR	F
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A 38 YEAR OLD FEMALE PATIENT IN FRANCE IN AN OPEN-LABEL VIRAMUNE CLINICAL TRIAL (TRIANON, 1100.1219, PATIENT NO. 08503) BEGAN VIRAMUNE TABLETS ON 29DEC97. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES STAVUDINE (D4T) AND INDINAVIR SINCE 29DEC97. PREVIOUS MEDICAL HISTORY WAS NOT REPORTED. SINCE BEGINNING ANTIRETROVIRAL THERAPY SHE HAS HAD A FEVER WHICH WAS TREATED WITH ANTIBIOTICS AND ANTIPYRETICS. HER ANTIRETROVIRAL THERAPY WAS INTERRUPTED AND THE FEVER DISAPPEARED. THE FEVER REAPPEARED WHEN THERAPY WAS REINTRODUCED. THE DATES OF DECHALLENGE/RECHALLENGE WERE NOT REPORTED. IN APR98 SHE DEVELOPED A SINUSITIS. ON 05MAY98 THE PATIENT WAS HOSPITALIZED WITH A FEVER AND RIGORS. THE INTENSITY OF THE EVENTS WAS REPORTED TO BE SEVERE. VIRAMUNE WAS DISCONTINUED ON 06MAY98. TREATMENT FOR THE EVENTS WAS NOT REPORTED. THE PATIENT RECOVERED ON 07MAY98. STAVUDINE AND INDINAVIR WERE CONTINUED. BOTH THE INVESTIGATOR AND THE CLINICAL MONITOR JUDGED THERE WAS A REASONABLE POSSIBILITY THAT THE EVENTS WERE RELATED TO THE TRIAL MEDICATION.

1998-001519	16JUN1998	INITIAL	SUDDEN INFANT DEATH SYNDROME	DY	M
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THE ANTIRETROVIRAL PREGNANCY REGISTRY RECEIVED INFORMATION FROM GLAXO-WELLCOME IN SWEDEN REGARDING A MALE INFANT (NO. 25209) THAT DIED ON THE 37 YEAR OLD WHITE BIRTH MOTHER

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

HAD BEEN TAKING ZIDOVUDINE AND LAMIVUDINE FOR AN ASYMPTOMATIC HIV INFECTION WITH A LOW CD4 ---

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
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1998-1519 cont'd
COUNT (200-400 U/L) SINCE 15MAY96. SHE REPORTEDLY WAS ON ZIDOVUDINE AND LAMIVUDINE AT THE TIME OF CONCEPTION AND DELIVERY. THE DATE OF HER LAST MENSTRUAL PERIOD WAS 25FEB97. AN ULTRASOUND PROVIDED AN ESTIMATED DATE OF DELIVERY TO BE _____ THE BIRTH MOTHER RECEIVED THERAPY WITH VIRAMUNE FROM 15NOV97 TO 20NOV97. ON 20NOV97 SHE RECEIVED INTRAVENOUS ZIDOVUDINE (DOSING 1-2 MG/KG/HR) AS PROPHYLAXIS AGAINST MATERNAL/FETAL HIV TRANSMISSION. SHE DELIVERED A MALE INFANT BY CAESAREAN SECTION AT 37 WEEKS GESTATION (EXACT DATE OF BIRTH UNKNOWN). THE INFANT WEIGHED 2855 GRAMS WITH A HEAD CIRCUMFERENCE OF 33.5 CM. NO BIRTH DEFECTS WERE NOTED. FOR APPROXIMATELY TWO WEEKS NEONATAL WITHDRAWAL SYMPTOMS WERE PRESENT. THE INFANT DIED UNEXPECTEDLY AT HOME ON _____ THE CAUSE OF DEATH WAS REPORTED TO BE SUDDEN INFANT DEATH SYNDROME. IT IS UNKNOWN WHETHER AN AUTOPSY WAS PERFORMED. HEPATITIS C, METHADONE AND POSSIBLY OTHER TRANQUILIZERS WERE REPORTED TO HAVE POTENTIALLY IMPACTED ON THE OUTCOME OF THE PREGNANCY.

1998-001557	18JUN1998	INITIAL	PANCREATITIS	28	YR F
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A 28 YEAR OLD FEMALE PATIENT IN FRANCE IN A COMPASSIONATE USE VIRAMUNE CLINICAL TRIAL BEGAN VIRAMUNE THERAPY ON 27JAN98 COMBINED WITH STAVUDINE, ABACAVIR, AND DIDANOSINE. ON 14APR98 THE PATIENT EXPERIENCED PANCREATITIS (SERUM AMYLASE 1.35 TIMES NORMAL RATE, SERUM LYPASE 3.1 TIMES NORMAL RATE). VIRAMUNE WAS DISCONTINUED (14APR98). ON 17APR98, THE PATIENT'S SERUM AMYLASE WAS 11.43 TIMES NORMAL RATE AND HER SERUM LYPASE WAS 8.3 TIMES NORMAL RATE. ON 04MAY98, THE SERUM AMYLASE RATE HAD RETURNED TO A NORMAL LEVEL AND THE SERUM LYPASE RATE WAS 4.36 TIMES NORMAL RATE. THE PATIENT RECOVERED. THE INVESTIGATOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENT WAS CAUSED BY VIRAMUNE, WHILE THE CLINICAL MONITOR FELT THERE WAS NO REASONABLE POSSIBILITY THE VIRAMUNE CAUSED THE EVENT.

FD E97-1278	07APR1998	INITIAL	EPIDERMAL NECROLYSIS		YR M
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A PATIENT IN ENGLAND IN AN EXPANDED ACCESS VIRAMUNE TRIAL BEGAN VIRAMUNE ON 25APR97. ON 06JUN97 THE PATIENT DEVELOPED SYMPTOMS INCLUDING, EXUDATIVE DERMATITIS, PHARYNGITIS, SORE THROAT, MACULOPAPULAR RASH, SPREADING OVER THE FACE, ARMS AND LEGS AND RESULTING IN BLISTERING, WITH A TEMPERATURE OF 38C, COUGH (BROWN SPUTUM WITH STREAK OF BLOOD). THE DIFFERENTIAL DIAGNOSIS WAS OF STEVENS JOHNSON SYNDROME DUE TO VIRAMUNE WITH SCALDED SKIN OR STAPHYLOCOCCAL/STREPTOCOCCAL INFECTION. A BLOOD SAMPLE HAD CULTURED MRSA (METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS). HOWEVER DISCUSSIONS BETWEEN THE CLINICAL MONITOR AND REPORTER CONCLUDED THAT THIS WAS UNLIKELY. THE PATIENT WAS ADMITTED TO THE HOSPITAL. VIRAMUNE WAS STOPPED AND FOR A WHILE THE RASH GOT WORSE INVOLVING HANDS, FEET, ARMS AND LEGS MAINLY. THE PATIENT WAS ALSO SEEN BY A DERMATOLOGIST WHO STATED THE SYMPTOMS COULD POSSIBLY BE DUE TO HERPES ZOSTER INFECTION, HOWEVER AGAIN THIS WAS THOUGHT TO BE UNLIKELY AND NO ANTI-HERPETIC TREATMENT WAS STARTED. THE FINAL DIAGNOSIS MADE WAS STEVENS JOHNSON REACTION/TOXIC EPIDERMAL NECROLYSIS. TREATMENT WITH MEROPENEM 500 MG TID IV FOR 4 DAYS WAS PRESCRIBED. VIRAMUNE WAS DISCONTINUED ON 09JUN97 AS WAS EPIVIR (LAMIVUDINE). SYMPTOMS STARTED TO RESOLVE WITHIN 24 HOURS OF DISCONTINUATION. THE PATIENT WAS DISCHARGED FROM THE HOSPITAL AND WAS DUE TO RETURN TO THE OUTPATIENT CLINIC ON 19JUN97. THE CLINIC VISIT NOTED THAT THE PATIENT IS NOW FINE AND COMPLETELY RECOVERED FROM THE EVENT. THIS EVENT HAS BEEN RECODED TO TOXIC EPIDERMAL NECROLYSIS. THE INVESTIGATOR AND THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENT WAS CAUSED BY VIRAMUNE.

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
1998-000293	08APR1998	FOLLOW-UP	ANOREXIA NAUSEA GAMMA-GT INCREASED JAUNDICE WEIGHT DECREASE	41 YR	M

A 41 YEAR OLD MALE PATIENT IN FRANCE BEGAN TREATMENT (EXPANDED ACCESS) WITH VIRAMUNE TABLETS, DIDANOSINE, AND STAVUDINE ON 02DEC97. THE PATIENT HAS A PRIOR HISTORY OF HEPATITIS C AND ALCOHOLISM. ONE MONTH AFTER TREATMENT WITH 400 MG/DAY OF VIRAMUNE, HE DEVELOPED ANOREXIA WITH LOSS OF WEIGHT AND NAUSEA. ON 30DEC97, THE PATIENT PRESENTED WITH JAUNDICE AND INCREASED GAMMA-GT (GGT). AN ABDOMINAL ECHOGRAPHY WAS PERFORMED, THE RESULT WAS NORMAL. ALL TREATMENTS WERE STOPPED ON 30DEC97 AND THE PATIENT RECOVERED ON 11JAN98.

1998-000298	01JUN1998	FOLLOW-UP	FEVER HEPATOSPLENOMEGALY AGRANULOCYTOSIS HEPATIC FAILURE COUGHING JAUNDICE SWEATING INCREASED RASH MACULO-PAPULAR	38 YR	M
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A PHYSICIAN REPORTED THAT A 38 YEAR OLD WHITE MALE PATIENT BEGAN ANTIRETROVIRAL THERAPY WITH VIRAMUNE, ZERIT, INVIRASE AND NORVIR ON 22DEC97. THE PATIENT HAD PREVIOUSLY BEEN ON LAMIVUDINE, STAVUDINE AND NELFINAVIR. ANTIRETROVIRAL THERAPY WAS CHANGED TO THE PRESENT REGIMEN AFTER HIS VIRAL LOAD INCREASED TO 5000 COPIES AND HIS CD4 COUNT WAS 234 CELLS/MM3 (DEC97). CONCOMITANT MEDICATION INCLUDED DIFLUCAN SINCE AUG95, DAPSONE SINCE 1995 AND A VARIETY OF HOLISTIC MEDICATIONS. HE HAS A MEDICAL HISTORY OF ALCOHOL AND INTRAVENOUS DRUG ABUSE, CHRONIC HEPATITIS-C, LAENNEC'S CIRRHOSIS AND PNEUMOCYSTIS. ON 06JAN98 HE DEVELOPED A MILD RASH WHICH WAS TREATED SYMPTOMATICALLY. ON 20JAN98 HE DEVELOPED A FEVER (TEMPERATURE 101 DEGREES FAHRENHEIT), SWEATS, A COUGH AND AN ERYTHEMATOUS MACULOPAPULAR RASH WAS NOTED. LABORATORY TESTS REVEALED A TOTAL BILIRUBIN (T BILI) 1.8 MG/DL, ALKALINE PHOSPHATASE (ALK PHOS) OF 128 U/L, GAMMA-GLUTAMYL TRANSFERASE (GGT) 165 U/L, ASPARTATE AMINOTRANSFERASE (AST) 154 U/L, ALANINE AMINOTRANSFERASE (ALT) 136 U/L, URIC ACID 3.7 MMOL/L. THE ELEVATED LIVER FUNCTION VALUES WERE REPORTED TO BE BASELINE FOR THE PATIENT. VIRAMUNE WAS DISCONTINUED AT THIS TIME. ON 28JAN98 LABORATORY TESTS REVEALED AST OF 343 U/L, ALT 389 U/L, GGT 145 U/L, T BILI 10.2 MG/DL, CD4 COUNT OF 126 CELLS/MM3, HEPATITIS C VIRUS RNA 1686 COPIES/ML. ON 29JAN98 HE WAS FEBRILE WITH A TEMPERATURE OF 102 DEGREES FAHRENHEIT (2 HOURS) AFTER TAKING IBUPROFEN. HE REPORTED HAVING A FEVER OVER MOST OF THE PAST WEEK, COMPLAINED OF MILD ABDOMINAL DISCOMFORT AND WAS JAUNDICED. ALL MEDICATIONS WERE DISCONTINUED EXCEPT DAPSONE AND AMBIEN. NORVIR WAS REPORTED TO BE AN ALTERNATE SUSPECT DRUG. ON 30JAN98 HE WAS HOSPITALIZED WITH FEVER, INCREASING JAUNDICE AND ABDOMINAL PAIN. HE WAS FOUND TO HAVE AN AGRANULOCYTOSIS JUDGED BY HIS PHYSICIAN MOST LIKELY SECONDARY TO VIRAMUNE, AND ACUTE/CHRONIC HEPATITIS. AN ULTRASOUND AND CT REVEALED SOME ASCITIS AND A THICKENED GALLBLADDER WITH NO EVIDENCE OF ACUTE CHOLECYSTITIS. HE WAS STARTED ON UNASYN AND GIVEN HIGH DOSE CORTICOSTEROIDS. HIS PROLONGED PROTHROMBIN TIME (20.8 SECONDS ON 28JAN98) RESPONDED TO VITAMIN K THERAPY. HE DEFERVESCED AND IMPROVED CONSIDERABLY. ON 30JAN98 HIS WHITE BLOOD CELL COUNT (WBC) WAS 2.6 K/UL WITH NO GRANULOCYTES. WITHIN 48 HOURS OF ADMISSION HE BEGAN TO REDEVELOP GRANULOCYTES AND ON 02FEB98 HIS WBC WAS 3.1 K/UL WITH APPROXIMATELY 1/3 RD MATURE GRANULOCYTES. T BILI WAS EXTREMELY HIGH THROUGHOUT HOSPITALIZATION (23.8 MG/DL ON 01FEB98); ALT WAS 232 U/L ON 31JAN98, 179 U/L ON 02FEB98; AST 193 U/L ON 30JAN98, 83 U/L ON 02FEB98; ALK PHOS 145 U/L ON 30JAN98, 153 ON 01FEB98. BLOOD

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

A 49 YEAR OLD MALE PATIENT IN AUSTRALIA BEGAN THERAPY WITH VIRAMUNE ON 08JAN98 FOR AN HIV-1 INFECTION. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES 500 MG OF ZIDOVUDINE TAKEN FOR 2 YEARS AND 300 MG OF LAMIVUDINE TAKEN FOR 14 MONTHS. BEFORE VIRAMUNE, THE PATIENT HAD BEEN TAKING SAQUINAVIR, ZIDOVUDINE AND LAMIVUDINE. AT THE TIME OF THE EVENT VIRAMUNE DOSING WAS 400 MG DAILY. ON 28JAN98 THE PATIENT EXPERIENCED MALAISE, JAUNDICE AND ABNORMAL URINE (DARK URINE). ON 02FEB98 LABORATORY VALUES WERE: ALKALINE PHOSPHATASE (ALP)-945 U/L, ASPARTATE TRANSAMINASE

MANUFACTURER CONTROL NUMBER	SUBMIT DATE	SUBMIT TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX
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1998-000369 cont'd
(AST)-186 U/L, ALANINE TRANSAMINASE (ALT)-349 U/L, BILIRUBIN (BIL)-207, GAMMA-GLUTAMYL TRANSFERASE (GAMMA GT)-1266 U/L, EOSINOPHILS-0.5 (10 TO THE POWER OF 9) AND HE WAS DIAGNOSED WITH CHOLESTATIC HEPATITIS. NO OTHER CONCOMITANT MEDICATIONS OR DISEASES WERE REPORTED. ALTHOUGH THE PATIENT RECEIVED THERAPY AS AN OUTPATIENT, THE REPORTING PHYSICIAN CLASSIFIED THE CHOLESTATIC HEPATITIS AS SERIOUS AND OF MODERATE INTENSITY BECAUSE THIS EVENT REQUIRED TREATMENT. VIRAMUNE WAS DISCONTINUED ON 20FEB98. ZIDOVUDINE AND LAMIVUDINE WERE CONTINUED. THE EVENTS WERE REPORTED TO HAVE RESOLVED IN 6 WEEKS. ON 04MAR98 LABORATORY VALUES WERE: ALP-147, AST-21, ALT-23, BIL-37 AND GAMMA GT-343.

FD E97-1326 02APR1998 FOLLOW-UP RENAL FUNCTION ABNORMAL 45 YR M

A PHYSICIAN IN AUSTRALIA REPORTED THAT A 45 YEAR OLD WHITE MALE PATIENT WITH A PAST HISTORY OF PYELONEPHRITIS TAKING VIRAMUNE, SAQUINAVIR, D4T, AND 3TC DEVELOPED RENAL FAILURE. THE PATIENT HAD BEEN TAKING VIRAMUNE (400 MG) SINCE 05MAY97 WITH NO APPARENT RENAL TOXICITY UP TO HIS LAST VISIT (26MAY97). AT THE TIME OF HIS LAST VISIT (26MAY97) CONCOMITANT MEDICATIONS TAKEN INCLUDED SAQUINAVIR, STAVUDINE, LAMIVUDINE, PREDNISONE, ETHAMBUTOL, CLARITHROMYCIN, AND MAGNESIUM SUPPLEMENTS. THE LAST LABORATORY TEST FOR RENAL FUNCTION WAS IN NOVEMBER 1996 WHEN BOTH SERUM CREATININE (0.070 MMOL/L, NORMAL RANGE 0.006-0.12) AND SERUM UREA (5.0, NORMAL RANGE 3.4-8.0) VALUES WERE NORMAL. THE PATIENT STARTED TO GO INTO RENAL FAILURE ON 10JUN97 AND EXPIRED ON 13JUN97. NO AUTOPSY WAS PERFORMED. THE PHYSICIAN HAS INDICATED THAT THERE IS NO POSSIBILITY OF A CAUSAL RELATIONSHIP TO VIRAMUNE. IN FOLLOW-UP INFORMATION RECEIVED ON 13FEB98, THE PATIENT'S PHYSICIAN REPORTED THAT AT THE TIME OF HOSPITALIZATION THE PATIENT WAS ALSO VERY SIGNIFICANTLY PANCYTOPENIC AND PROBABLY SEPTIC. ON 10JUN97 THE PATIENT SUDDENLY BECAME SHORT OF BREATH AND WENT INTO A FLUID OVERLOAD DUE TO A SIGNIFICANTLY DEPRESSED ALBUMIN. HIS CREATININE WAS WITHIN NORMAL LIMITS. HE ADDITIONALLY DEVELOPED ATRIAL FLUTTER WITH A 2:1 BLOCK. THIS WAS FELT TO BE RELATED TO HYPOKALEMIA, WHICH WAS FELT TO BE RELATED TO FOSCARNET THERAPY. HE DETERIORATED FURTHER AND BECAME HYPERTENSIVE. FURTHER IV ANTIBIOTICS WERE GIVEN AS WELL AS INTRAGAM TO HELP ASSIST WITH HIS LOW PLATELET COUNT. HE WAS ALSO GIVEN PLATELET TRANSFUSION AND PACKED CELLS FOR HIS ANEMIA. ON 11JUN97 HE HAD A DROP IN HIS HEMOGLOBIN AND A RISE IN HIS CREATININE WITH A TENDER ABDOMEN. IT WAS CLINICALLY FELT HE MAY HAVE HAD AN INTRA-ABDOMINAL BLEED. IT WAS DECIDED TO TREAT THE PATIENT ONLY WITH PALLIATIVE CARE. THE VIRAMUNE THERAPY AND ALL ANTIVIRALS WERE DISCONTINUED SEVERAL WEEKS PRIOR TO HIS HOSPITALIZATION OF 05JUN97. FOLLOW-UP INFORMATION RECEIVED ON 11MAR98 FROM THE HOSPITAL PHYSICIAN REPORTED THAT THE PATIENT TOOK HIMSELF OFF ALL MEDICATION BETWEEN 26MAY97 AND 05JUN97. THE PATIENT DID NOT INFORM ANYONE OF THE DATE.

FD E97-2013 12JUN1998 FOLLOW-UP ALOPECIA 39 YR M
RASH
CONJUNCTIVAL DISCOLOURATION
RENAL FUNCTION ABNORMAL
THROMBOCYTOPENIA
LYMPHADENOPATHY CERVICAL
OEDEMA
FEVER
LEUCOPENIA
RIGORS
RIGORS

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

A 39 YEAR OLD ORIENTAL MALE PATIENT IN JAPAN IN AN OPEN LABEL VIRAMUNE TRIAL, BEGAN VIRAMUNE TABLETS ON 08SEP97. ADDITIONAL ANTIRETROVIRAL THERAPY INCLUDES EPIVIR (SINCE APR97) AND ZERIT (ONSET DATE OF THERAPY NOT REPORTED). OTHER CONCOMITANT DRUG THERAPY INCLUDES VOLTAREN SR AND SELBEX SINCE APR97. CONCOMITANT DISEASES INCLUDE CONGENITAL HEMOPHILIA A, HEMOPHILIC ARTHROSIS AND HEPATITIS C. ON 08SEP97 THE PATIENT'S CREATININE WAS 0.7 MG/DL, BUN 13 MG/DL, C-REACTIVE PROTEIN (CRP) 0.1 MG/DL. ON 14SEP97 THE PATIENT HAD A TEMPERATURE OF 37.2 C.

MANUFACTURER	SUBMIT	SUBMIT			
CONTROL NUMBER	DATE	TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX

FD E97-2013 cont'd

RISING TO 38 C ON 15SEP97. VOLTAREN SUPPOSITORIES WERE PRESCRIBED. ON 16SEP97, HE EXPERIENCED RIGORS AND SHIVERING, AND HIS CRP INCREASED TO 9.1 MG/DL. ON 17SEP97 AN ERYTHEMATOUS RASH (WITHOUT SWELLING) DEVELOPED ON HIS FACE, TRUNK AND LIMBS. HE ALSO DEVELOPED BULBAR CONJUNCTIVA HYPEREMIA, GENERALIZED EDEMA AND SWOLLEN CERVICAL LYMPH NODES. VIRAMUNE AND OTHER CONCOMITANT DRUGS WERE DISCONTINUED ON 17SEP97. THE RASH BECAME CONFLUENT AND THE PATIENT EXPERIENCED A DECREASED URINARY OUTPUT WITH A RISE IN CREATININE TO 2.0 MG/DL. ON 18SEP97 THE PATIENT'S FEVER AND CUTANEOUS SYMPTOMS PERSISTED. LABORATORY VALUES REVEALED AN INCREASE IN CRP TO 28 MG/DL, CREATININE TO 2.1 MG/DL, BUN 33 MG/DL. HE WAS GIVEN INTRAVENOUS (IV) SOLU-CORTEF (500 MG). THE PATIENT WAS HYDRATED 2300ML/DAY FOR FURTHER DECREASE IN URINARY OUTPUT. ON 19SEP97 THE URINE VOLUME INCREASED WITH CREATININE OF 2.0 MG/DL, BUN 39 MG/DL, CRP 26.5 MG/DL AND HIS PLATELETS HAD DECREASED TO 109,000/MM3. THE RASH HAD NOT RECOVERED AND IV SOLU-MEDROL 500 MG WAS ADMINISTERED. ON 20SEP97 THE FEVER, RIGORS, SHIVERING, BULBAR CONJUNCTIVA HYPEREMIA AND CERVICAL LYMPH NODE SWELLING HAD RESOLVED. BETWEEN 20SEP97 AND 27SEP97 INTRAVENOUS STEROIDS WERE ADMINISTERED IN TAPERING DOSES. ON 21SEP97 THE PATIENT'S DECREASED RENAL FUNCTION RESOLVED. CREATININE WAS 0.9 MG/DL, BUN 17 MG/DL, CRP 4.3 MG/DL. ON 23SEP97 THE PATIENT DEVELOPED LEUCOPENIA WITH A WHITE BLOOD CELL COUNT (WBC) OF 2,900/MM3. ON 24SEP97 HIS PLATELET COUNT IMPROVED TO 155,000/MM3 AND THE WBC INCREASED TO 4,900/MM3. ON 27SEP98 THE PATIENT DEVELOPED ALOPECIA DUE TO A "CUTANEOUS DISORDER". ON 13OCT97 THE RASH AND EDEMA DISAPPEARED. ON 12JAN98 THE ALOPECIA RESOLVED. ACCORDING TO THE INVESTIGATOR, THE RASH, GENERALIZED EDEMA AND RENAL FUNCTION DISORDERS WERE SERIOUS BECAUSE THEY PROLONGED HOSPITALIZATION. THE EVENTS THROMBOCYTOPENIA, LEUCOPENIA, BULBAR CONJUNCTIVA HYPEREMIA, SWOLLEN CERVICAL LYMPH NODES, ALOPECIA, RIGORS, AND SHIVERING WERE REPORTED TO BE NON-SERIOUS. THE INVESTIGATOR JUDGED THERE WAS A REASONABLE POSSIBILITY THAT ALL EVENTS WERE RELATED TO THE TRIAL MEDICATION. HE CONSIDERED THE RENAL FUNCTION AND EDEMA TO BOTH BE CAUSED A "DIAPYEDESIS OF SERUM". THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENTS WERE CAUSED BY THE TRIAL DRUG.

FD E97-2250 08APR1998 FOLLOW-UP EPIDERMAL NECROLYSIS 35 YR M
03JUN1998 FOLLOW-UP

A PHYSICIAN REPORTED THAT A 35 YEAR OLD MALE PATIENT IN A COMPASSIONATE USE STUDY IN FRANCE, BEGAN THERAPY WITH VIRAMUNE ON 23OCT97 FOR AN HIV INFECTION. CONCOMITANT MEDICATIONS INCLUDED 1 GM NORVIR AND 500 MG RETROVIR, DAILY, BOTH STARTED ON 23OCT97 AND 2 GM ORACEFAL (CEFADROXIL), DAILY, STARTED ON 03NOV97 FOR PHARYNGITIS. ON 04NOV97 THE PATIENT DEVELOPED LYELL SYNDROME, WHICH WAS CONSIDERED IMMEDIATELY LIFE-THREATENING, AND WAS HOSPITALIZED. ORACEFAL WAS DISCONTINUED ON 04NOV97. VIRAMUNE, NORVIR AND RETROVIR WERE DISCONTINUED ON 05NOV97. AN INFECTIOUS MONONUCLEOSIS WAS DIAGNOSED ON 06NOV97 (POSITIVE SEROLOGY). ON 24NOV97 FOLLOW-UP INFORMATION RECEIVED INDICATED THE PATIENT RECOVERED (DATE UNKNOWN). THE PATIENT WAS NOT INCLUDED IN THE EXPANDED ACCESS PROGRAM. THE PHYSICIAN USED THE TREATMENT OF ANOTHER PATIENT. THE PHYSICIAN THINKS THAT THE ADVERSE EVENT IS RELATED TO VIRAMUNE AND/OR ORACEFAL AND/OR NORVIR. AFTER A DISCUSSION WITH THE FRENCH DRUG AGENCY THE PATIENT HAS BEEN RETROSPECTIVELY INCLUDED INTO THE EXPANDED ACCESS PROGRAM. COMMENT IS: "REPORTED AS TEN. NO INFORMATION ON CLINICAL PATTERN".

SECTION III.F. NARRATIVE SUMMARY AND ANALYSIS OF INFORMATION

FD E97-2472 03JUN1998 FOLLOW-UP EPIDERMAL NECROLYSIS 40 YR M

A 40 YEAR OLD MALE IN FRANCE IN AN EXPANDED ACCESS VIRAMUNE TRIAL (1100.1225, PATIENT NUMBER 1458) BEGAN TRIAL DRUG 14NOV97. THE PATIENT WAS ALSO RECEIVING TREATMENT WITH ABACAVIR COMBINED WITH ZIDOVUDINE, ZALCITABINE AND NELFINAVIR. ON 06DEC97, HE REQUIRED HOSPITALIZATION FOR STEVENS-JOHNSON SYNDROME APPEARING WITH LESIONS OF GENITAL MUCOUS MEMBRANE, CONJUNCTIVITIS, OESOPHAGITIS, SCATTERED BULLAE ON THE BODY PLUS ZONE OF SAFE SKIN. WITHOUT ---

MANUFACTURER	SUBMIT	SUBMIT			
CONTROL NUMBER	DATE	TYPE	ADVERSE EVENT TERMS (BI WHOART)	AGE	SEX

FD E97-2472 cont'd

MORE INFORMATION IT IS SUSPECTED THAT THE EXTENT OF EPIDERMAL DETACHMENT WAS PROBABLY LESS --- THAN 30% OF THE BODY SURFACE AREA. VIRAMUNE WAS DISCONTINUED ON 06DEC97. ON 23JAN98, THIS EVENT WAS RECODED TO LYELL SYNDROME. THE PATIENT'S STATUS WAS STABILIZED, AND HE RECOVERED ON 05JAN98. THE INVESTIGATOR AND THE CLINICAL MONITOR FELT THERE WAS A REASONABLE POSSIBILITY THE EVENT WAS RELATED TO THE TRIAL DRUG.

MVIR 12/03/97 11JUN1998 FOLLOW-UP THINKING ABNORMAL 12 YR F

A PHYSICIAN REPORTED A 12 YEAR OLD FEMALE WITH A HISTORY OF RENAL FAILURE, HAS BEEN ON VIRAMUNE THERAPY FOR SEVERAL MONTHS. SHE REQUIRES DIALYSIS 3 TIMES WEEKLY. SHE IS ALSO TAKING ZERIT AND NELFINAVIR CONCOMITANTLY. ON 02DEC97 DURING DIALYSIS THE PATIENT DEVELOPED ABNORMAL MOVEMENTS AND WAS NOT ALERT AND ORIENTED TO PERSON, PLACE OR TIME. THE PATIENT WAS DIAGNOSED WITH ENCEPHALOPATHY BASED ON CHANGE IN MENTAL STATUS. THE SYMPTOMS RESOLVED MOMENTARILY BUT HAVE SINCE RETURNED. A NEUROLOGY CONSULT WAS ORDERED. THE PATIENT REMAINS HOSPITALIZED. VIRAMUNE WAS CONTINUED. FOLLOW-UP INFORMATION HAS BEEN RECEIVED ON 04FEB98 FROM THE PATIENT'S PHYSICIAN, WHICH REPORTED THAT AFTER FURTHER EVALUATION, IT SEEMED THAT THE PATIENT'S ENCEPHALOPATHY WAS PSYCHOGENIC AND NOT ORGANIC.

**APPEARS THIS WAY
ON ORIGINAL**