MEMORANDUM

Date: July 10, 2002

To: Antiviral Drug Products Advisory Committee Members and Guests

From: Adefovir Review Team

Through: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products

Mark Goldberger, M.D., M.P.H.
Office of Drug Evaluation 4

Subject: Briefing document for NDA 21-449: Adefovir dipivoxil

This document provides background and a preliminary FDA perspective on the upcoming Antiviral Drug Products' Advisory Committee meeting on August 6, 2002. At this meeting, we will ask Committee members and guests to discuss the New Drug Application (NDA # 21-449) submitted by Gilead Sciences, Inc., for adefovir dipivoxil (hereinafter, "adefovir" or "ADV") for the treatment of chronic hepatitis B (CHB) in adults.

Executive Summary

The applicant previously studied adefovir (at doses of 60 to 500 mg daily) for the treatment of human immunodeficiency virus (HIV) infection. After an Advisory Committee meeting in November 1999, the Division of Antiviral Drug Products issued a nonapprovable letter to the applicant's marketing application for adefovir for the treatment of HIV infection. This action was primarily based on the drug's unacceptable nephrotoxicity profile and overall unfavorable risk-benefit profile at the studied doses. A significant proportion of HIV-infected patients who took adefovir at 60 mg daily or 120 mg daily doses experienced serum creatinine increases and hypophosphatemia.

The clinical development of adefovir for chronic hepatitis B began with lower does of adefovir. Study GS-98-437 employed adefovir 10 mg daily and 30 mg daily in HBeAg-positive patients who had adequate baseline renal function. It became apparent during this study, however, that the adefovir 30 mg daily dose was associated with an increased risk of nephrotoxicity compared with the adefovir 10 mg daily dose. The second pivotal study, GS-98-438, focused only the adefovir 10 mg daily dose in HBeAg-negative patients who also had adequate renal function at baseline. The applicant now requests approval of adefovir at a dose of 10 mg daily for the treatment of chronic hepatitis B.

Our analysis of results from studies GS-98-437 and GS-98-438 showed that patients in the adefovir-treated groups had statistically significant histologic improvement compared

with those in the placebo group. The adverse event profiles of adefovir-treated groups, particularly the adefovir 10 mg group, were not significantly different from the placebo group. Patients receiving adefovir had a lower incidence of elevated liver enzymes compared to those receiving placebo. As stated above, a substantial proportion of patients receiving the adefovir 30 mg daily dose of adefovir developed serum creatinine increases sometimes associated with hypophosphatemia. Few patients in the adefovir 10 mg group had elevated serum creatinine levels and none had confirmed grade 2 (moderate) hypophosphatemia.

Of note, the Division's analysis of safety data from study GS-98-435, an open-label study to evaluate the adefovir 10 mg daily dose (or 5 mg daily dose in some cases) in patients status post liver transplantation or on a waiting list for liver transplantation, revealed evidence of treatment-emergent nephrotoxicity in a number of patients with pre-existing renal function impairment. Data on this issue will be presented in detail below. We believe that the data merit further discussion by the Committee.

The following is a summary of relevant clinical data on the effectiveness and safety of adefovir in chronic hepatitis B patients with emphases on the two "pivotal" controlled studies, GS-98-437 and GS-98-438, and the open-label study GS-98-435. Data on other small "supportive" clinical studies (studies GS-94-404, GS-96-412, GS-96-413, GS-99-460i, GS-99-465, and GS-00-461) were either incompletely submitted or not submitted to this NDA, and thus, they will not be reviewed in detail in this background document. Please refer to the applicant's briefing document for a summary of these studies.

1. Summary of Principle Clinical Studies

A summary of the study designs of studies GS-98-437, GS-98-438, and GS-98-435 is presented in Table 1A. Study GS-98-435 is an uncontrolled study with a complex design that includes both cohorts and subcohorts. It enrolled patients who were status post liver transplantation or patients on a waiting list for liver transplantation. Cohort 1 included patients with adequate renal, hepatic, and hematologic function at the time of enrollment. Cohort 3 included those with inadequate renal, hepatic, and hematologic function at baseline. A few patients from another liver transplant study (study GS-99-451i) rolled into cohort 2. Each of these cohorts was further subdivided into subcohort A for the post-liver transplantation patients and subcohort B for those wait-listed for a liver transplant.

Table 1A. Summary of Studies GS-98-437, GS-98-438, and GS-98-435

Study	Patient Population	Number of ITT Patients (dose)	Duration	Primary Endpoint
GS-98-437[1] - "Pivotal" - US and non-US study sites	- Compensated CHB, HBeAg+ - ALT ≥ 1.2 x upper limit normal - Serum creatinine ≤ 1.5 mg/dL - Serum HBV DNA ≥ 10^6 copies/mL	Year 1: 173 (30 mg) 171 (10 mg) 167 (placebo) Year 2: 223 (10 mg) 212 (placebo)	96 wks	Liver biopsy at wk 48
GS-98-438[1] - "Pivotal" - No US study sites	- Compensated CHB, HBeAg– - ALT ≥ 1.5 x ULN - Serum creatinine ≤ 1.5 mg/dL - Serum HBV DNA ≥ 10^5 copies/mL	Year 1: 123 (10 mg) 61 (placebo) Year 2: 139 (10 mg) 40 (placebo)	96 wks + 3-yr extension	Liver biopsy at wk 48
GS-98-435[2]	- Lamivudine-resistant HBV - Cohort 1: adequate renal, hepatic, hematologic function at baseline - Cohort 2: roll over from study GS-99-451I - Cohort 3: inadequate renal, hepatic, hematologic function at baseline - subcohort A: Post-liver transplant - subcohort B: Waitlisted for liver transplant	Cohort 1A: 117 Cohort 2A: 12 Cohort 3A: 67 Cohort 1B: 46 Cohort 2B: 2 Cohort 3B: 80 (ADV 10mg or 5 mg daily)	Until toxicity or death	$DAVG_{24}$[3]

[1] Randomized, double blind, placebo-controlled, multicenter study.
[2] Open label, multicenter study.
[3] Time-weighted average change in serum HBV DNA from baseline at week 24.

The demographics of studies GS-98-437 and GS-98-438 (a non-US study) showed a balanced distribution of patients across treatment groups as shown in Table 1B and 1C. However, the study population was predominantly comprised of Caucasian and Asian males. Of note, the US study sites in study GS-98-437 enrolled 10% "Black" (15 patients) and 2% "Other" (3 patients) patients. Considering the fact that African Americans and Hispanic Americans account for 31% and 5% of people with hepatitis B infection in the U.S. (1996 Viral Hepatitis Surveillance Program Report by the Centers for Disease Control and Prevention), it appears that African Americans and Hispanic Americans were underrepresented in the applicant's drug development program.

Table 1B. Patient Demographics in Study GS-98-437

Characteristic	Treatment Group			
	ADV 30 mg	ADV 10 mg	Placebo	Total
Number of randomized patients	173	172	170	515
Number of ITT patients[1]	173	171	167	511
Gender	129 (75%)	130 (76%)	119 (71%)	378 (74%)
Male, n (%)	44 (25%)	41 (24%)	48 (29%)	133 (26%)
Female, n (%)				
Race	64 (37%)	60 (35%)	60 (36%)	184 (36%)
Caucasian, n (%)	5 (3%)	8 (5%)	3 (2%)	16 (3%)
Black, n (%)	101 (58%)	102 (60%)	101 (60%)	304 (59%)
Asian, n (%)	3 (2%)	1 (< 1%)	3 (2%)	7 (1%)
Other				

Table 1C. Patient Demographics in Study GS-98-438

Characteristic	Treatment Group		
	ADV 10 mg	Placebo	Total
Number of randomized patients	123	62	185
Number of ITT patients	123	61	184
Gender	102 (83%)	50 (82%)	152 (83%)
Male, n (%)	21 (17%)	11 (18%)	32 (17%)
Female, n (%)			
Race	82 (67%)	40 (66%)	122 (66%)
Caucasian, n (%)	5 (4%)	1 (2%)	6 (3%)
Black, n (%)	36 (29%)	20 (33%)	56 (30%)
Asian, n (%)	0 (0%)	0 (0%)	0 (0%)
Other			

Of note, there was a significant number of protocol deviations in both studies GS-98-437 (649 deviations) and GS-98-438 (886 deviations). However, a review of the protocol deviations indicated that the study outcomes were not affected by these.

2. Summary of Effectiveness Data

2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the "pivotal" studies GS-98-437 and GS-98-438 was histological improvement, defined as ≥ 2-point decrease from baseline in the Knodell necroinflammatory score with no concurrent worsening of the fibrosis score at week 48. Please refer to the applicant's briefing document for results of the primary endpoint analyses in which inadequate or missing biopsies were assumed as non-improvement for both studies. In general, we agree with the applicant's analyses of data on the primary

endpoint (i.e., liver biopsy histology) and secondary endpoints (i.e., serum HBV DNA change from baseline and serum alanine aminotransferase normalization). Our analyses revealed minor discrepancies that do not affect the final conclusions, thus, they will not be presented here.

The applicant should be commended for its unprecedented and successful effort to obtain baseline and week 48 liver biopsies, i.e., 86% of patients in study GS-98-437 and 92% in study GS-98-438. Results of analyses based on adequate baseline and week 48 liver biopsy pairs (i.e., inadequate or missing biopsies were excluded) in studies GS-98-437 and GS-98-438 are summarized in Tables 2.1A and 2.1B, respectively.

Table 2.1A. Histologic Results in Study GS-98-437

	Treatment group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of adequate biopsy pairs	147	152	149
Improvement[1]	99 (67%)	89 (59%)	41 (28%)
No improvement	48 (33%)	63 (41%)	108 (72%)
p-value[2]	< 0.001	< 0.001	
Mean baseline score in:			
Necroinflammation	7.84 ± 2.82	7.37 ± 2.75	7.83 2.89
Fibrosis	1.71 ± 1.06	1.64 1.09	1.83 1.12
Mean change from baseline in:			
Necroinflammation score	-3.18 ± 3.28	-2.52 ± 3.24	-0.11 ± 3.07
Fibrosis score	-0.31 ± 0.80	-0.18 ± 0.83	-0.01 ± 0.85

[1] Defined as ≥ 2-point decrease from baseline in the Knodell necroinflammatory score with no concurrent worsening fibrosis score at week 48.
[2] Compared to placebo (Chi-Square tests)

Table 2.1B. Histologic Results in Study GS-98-438

	Treatment group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of adequate biopsy pairs	113 (91%)	56 (90%)
Improvement	78 (69%)	20 (36%)
No improvement	35 (31%)	36 (64%)
p-value[1]	< 0.0001	
Mean baseline score in:		
Necroinflammation score	7.73 ± 2.74	7.09 ± 2.71
Fibrosis score	1.88 ± 1.17	1.81 ± 1.14
Mean change from baseline in:		
Necroinflammation score	-3.42 ± 2.86	0.27 ± 3.19
Fibrosis score	-0.29 ± 0.74	0.12 ± 0.93

[1] Compared to placebo (Chi-Square tests)

Adefovir treatment resulted in clinically and statistically significant improvement of the Knodell necroinflammatory score at week 48 compared to placebo. However, based on the mean change in the Knodell fibrosis score at week 48, it is unclear whether adefovir treatment had an effect on the progression of fibrosis in the liver. Therefore, we performed additional analyses to evaluate the change in fibrosis score from baseline at week 48 in studies GS-98-437 and GS-98-438. Results of these analyses are shown in Tables 2.1C and 2.1D.

Table 2.1C. Changes in Fibrosis Based on Knodell Score and Ishak Score at Week 48 in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of adequate biopsy pairs	147	152	149
Knodell fibrosis score[1]			
Improved by ≥ 1 point	29 (20%)	27 (18%)	15 (10%)
Unchanged	113 (77%)	114 (75%)	118 (79%)
Worsened by ≥ 1 point	5 (3%)	11 (7%)	16 (11%)
Ishak fibrosis score[2]			
Improved by ≥ 1 point	61 (41%)	52 (34%)	28 (19%)
Unchanged	71 (48%)	83 (55%)	89 (60%)
Worsened by ≥ 1 point	15 (10%)	17 (11%)	32 (21%)

[1] Knodell fibrosis score: 0 = absence of fibrosis; 1 = fibrosis restricted to the portal area; 3 = bridging fibrosis; 4 = cirrhosis.

[2] Ishak fibrosis score: 0 = no fibrosis; 1 = fibrosis expansion of some portal areas; 2 = fibrosis expansion of most portal areas; 3 = fibrosis expansion of most portal areas with occasional portal-to-portal bridging; 4 = fibrosis expansion of portal areas with marked bridging; 5 = marked bridging with occasional nodules (incomplete cirrhosis); 6 = cirrhosis, probable or definite.

Table 2.1D. Changes in Fibrosis Based on Knodell Score and Ishak Score at Week 48 in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of evaluable biopsy pairs	113	56
Knodell fibrosis score		
Improved	19 (17%)	5 (9%)
Unchanged	92 (81%)	43 (77%)
Worsened	2 (2%)	8 (14%)
Ishak fibrosis score		
Improved	38 (34%)	8 (14%)
Unchanged	70 (62%)	28 (50%)
Worsened	5 (4%)	20 (36%)

Based on the Ishak fibrosis scores (which is more sensitive to subtle changes), in chronic hepatitis B patients who were HBeAg-positive (study GS-98-437), 60% of patients in the placebo group did not have appreciable changes in fibrosis after one year. Of the remaining patients, 21% experienced progression in disease stage (fibrogenesis) compared with 19% showing varying degrees of regression in disease stage (fibrolysis). There was a clear shift in the proportion of patients with disease progression to disease regression among those who received adefovir treatment. Numerically, more patients in the adefovir 30 mg group (41%) had regression of fibrosis than in the adefovir 10 mg group (34%), although the proportion of patients with worsening fibrosis was similar (10% and 11%, respectively).

In chronic hepatitis B patients who were HBeAg-negative (study GS-98-438), it is discouraging to note that within a year, a significantly greater number of patients in the placebo group experienced more fibrogenesis (36%) than fibrolysis (14%). Since the number of available biopsy pairs was fewer in the latter group (56 pairs versus > 100 pairs in other treatment groups), this observation should be interpreted with some caution. Nevertheless, this appears consistent with the clinical observation that HBeAg-negative chronic hepatitis B is characterized by continued necroinflammation in the liver and a more fluctuating disease course. In contrast, only 4% of patients who received adefovir treatment had progression in fibrosis compared to 34% with regression of fibrosis.

These observations appear to show that consecutive liver biopsies within a year of each other are a sensitive way to detect not only changes in necroinflammatory activity but also changes in fibrosis. The use of serum HBV DNA or ALT as endpoints in evaluating drug therapy for chronic hepatitis B would not show the drug's effect on the progression of fibrosis.

The primary endpoint of study GS-98-435 was the time-weighted average change in serum HBV DNA from baseline at week 24 ($DAVG_{24}$). At the time of NDA submission, virologic data on this study are still incomplete. Nevertheless, available results on

approximately 68% of patients suggest that adefovir treatment was effective in lowering serum HBV DNA to levels comparable to those observed in studies GS-98-437 and GS-98-438.

2.2. Secondary Efficacy Endpoints

Data on the secondary efficacy endpoints (serum HBV DNA and ALT levels) have been adequately presented in the applicant's briefing document; hence, they will not be presented in entirety here. Of note are the following:

- In study GS-98-437, a greater proportion of patients receiving adefovir achieved decreases in serum ALT levels during the study than in the placebo group. The proportion of patients with normalization of ALT was 54% in the adefovir 30 mg group, 47% in the adefovir 10 mg group, compared to16% in the placebo group. This treatment effect was even more pronounced in the adefovir 10 mg group in study GS-98-438 with 68% of patients showing normalized ALT compared to 28% in the placebo group. This difference between studies could also be due to the naturally fluctuating course of HBeAg-negative chronic hepatitis B.

- Adefovir treatment was associated with an increased rate of HBeAg seroconversion (defined as a loss of HBeAg and a gain of anti-HBe antibody). This occurred in 17% in the adefovir 30 mg group, 14% in the adefovir 10 mg group, and 9% in the placebo group at week 48. The rates of seroconversion in adefovir-treated groups were comparable to that observed in previous lamivudine studies. At present, it remains unclear whether adefovir-associated HBeAg seroconversion is durable after treatment is discontinued. Time to HBeAg seroconversion in study 437 is shown in Table 2.2.

Table 2.2. Time to HBeAg Seroconversion by Kaplan-Meier Estimate

	Treatment Group					
	ADV 30 mg (n = 163)		ADV 10 mg (n = 170)		Placebo (n = 161)	
	Cum. events	KM%	Cum. Events	KM%	Cum. events	KM%
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	1	1%	1	1%	0	0%
> Week 4 - week 8	9	6%	4	2%	0	0%
> Week 8 - week 12	13	8%	6	4%	1	1%
> Week 12 - week 16	16	10%	7	4%	4	3%
> Week 16 - week 20	17	10%	9	5%	4	3%
> Week 20 - week 24	17	10%	13	8%	4	3%
> Week 24 - week 28	18	11%	15	9%	5	3%
> Week 28 - week 32	18	11%	16	9%	7	4%
> Week 32 - week 36	20	12%	18	11%	11	7%
> Week 36 - week 40	22	14%	20	12%	12	8%
> Week 40 - week 44	22	14%	22	13%	13	8%
> Week 44 - week 48	26	17%	23	14%	14	9%

Unfortunately, due to misallocation of study drug in the second year of study GS-98-437, data on serum HBV DNA and ALT levels during the second 48 weeks were limited. Nevertheless, based on the available data on study GS-98-437 and those of study GS-98-438, it appears that patients who were randomized to receive adefovir 10 mg daily and continued to take adefovir 10 mg daily in the second 48 weeks continued to have further decreases in serum HBV DNA (generally less than 0.5 $\log_{10}$ copies/mL). Patients who switched from active treatment to placebo group experienced a prompt return of serum HBV DNA to baseline levels within 4 to 8 weeks.

3. Summary of Safety Data

The safety results of studies GS-98-437 and GS-98-438 have been adequately presented in the applicant's briefing document and, except as noted, will not be repeated here. In general, the adverse event profiles of adefovir-treated groups, particularly the adefovir 10 mg group, were not significantly different from that of the placebo. Additionally, the benefit of adefovir treatment was obvious in that fewer patients in the adefovir-treated groups had elevated liver enzymes.

Safety data from study GS-98-435, particularly that related to renal impairment, will be described in detail below. It is relevant to note the following information on the pharmacokinetics of adefovir. The mean area under the curve ($AUC_{0-\infty}$) of adefovir 60 mg daily in HIV infected patients was approximately1,150 ng.hr/mL and the C_{max} was 110 ng/mL. Based on adefovir's linear kinetics, estimated AUC and C_{max} for adefovir 30 mg is 600 ng.hr/mL and 60 ng/mL, respectively. In chronic hepatitis B patients with intact renal function, the mean AUC and C_{max} of adefovir following multiple oral doses of

adefovir 10 mg daily are 204 ng.hr/mL and 18.3 ng/mL, respectively. However, in non-chronic hepatitis B patients with varying degrees of renal function impairment, an adefovir 10 mg daily dose resulted in serum concentrations exceeding those observed for higher doses of adefovir (30 mg or 60 mg) as shown in Table 3. Therefore, patients with renal impairment are likely to be at increased risk of adefovir nephrotoxicity unless a dose adjustment is made.

Table 3. Pharmacokinetics of Adefovir in Patients with Renal Function Impairment in Study GS-00-473

Adefovir	Renal Function Status by Creatinine Clearance (mL/min)			
	Normal (> 80)	Mild (50-79)	Moderate (30-49)	Severe (< 30)
Mean* $AUC_{0-\infty}$ (ng.hr/mL)	197	261	420	1115
Mean* C_{max} (ng/mL)	18	22	27	51
Median CL_{renal} (mL/hr/Kg)	211	149	86	35
n	7	8	8	10

*Geometric mean

3.1. Deaths

3.1.1. Study GS-98-437

Two deaths were reported after the clinical data cutoff date in study GS-98-437. The first case involved a 55-year-old black male who died of non-Hodgkin lymphoma and HTLV-I infection. The patient developed an increase in serum creatinine from 0.8 mg/dL at baseline to 1.2 mg/dL approximately ten months into treatment with adefovir 30 mg daily. This event could have been possibly related to adefovir treatment. Prior to his demise, the patient also suffered acute renal insufficiency that was most likely due to hypercalcemia of malignancy. In the second case, a 69-year-old male with a history of cardiomyopathy who received placebo in the first 48 weeks and adefovir 10 mg daily in the second 48 weeks, died of acute cardiac failure.

3.1.2. Study GS-98-438

One death was reported after the clinical data cutoff date in study GS-98-438. The case involved a 47-year-old black male who developed hepatocellular carcinoma at the beginning of the second 48 weeks of treatment. Nevertheless, he completed 96 weeks of adefovir 10 mg daily, and began lamivudine treatment. He underwent a liver transplantation. Twenty-four hours after surgery, he developed acute renal failure, a collapsed hepatic artery and necrosis of the right hepatic lobe. He subsequently died of disseminated mycosis.

3.1.3. Study GS-98-435

As of February 28, 2002, 390 patients were enrolled in study 435. Of these, a total of 42 patients (11%) died. Eighteen were in subcohort A (post-liver transplantation) and 24 in subcohort B (waitlisted for liver transplantation). A number of patients had multiple terminal events that led to their demise, hence multiple causes of death. According to the applicant's report, only one death was considered by the investigator to be related to study drug. This patient died of hepatorenal syndrome. Nevertheless, several other deaths in this study may be of concern, particularly in light of the recently available pharmacokinetic results of adefovir in patients with impaired renal function. It is unclear whether adefovir may have contributed to nephrotoxicity in several patients experiencing terminal events. These cases are presented in Appendix A.

3.2. Nephrotoxicity

Nephrotoxicity was the treatment-limiting toxicity of adefovir dipivoxil therapy at doses of 60 mg and 120 mg daily in clinical studies (GS-96-408, GS-97-417) involving human immunodeficiency virus (HIV)-infected patients (NDA 20-993). The toxicity is characterized by gradual increases of serum creatinine and, at times, decreases in serum phosphorus, with a delayed onset for both at a median of approximately 28 to 32 weeks (Q1-Q3 range of 20-39 weeks) of treatment. These abnormalities can be accompanied in some patients by changes in serum bicarbonate, glycosuria, and aminoaciduria, (or Fanconi syndrome). Approximately 34% of patients (by Kaplan-Meier estimates) who received adefovir 60 mg daily had serum creatinine increases of 0.5 mg/dL or greater at week 50 in study GS-97-417, compared to 42% who received adefovir 120 mg daily. Approximately 26% of patients in the adefovir 60 mg group and 49% in the adefovir 120 mg group had serum phosphorus levels of < 2.0 mg/dL at week 50 of treatment.

3.2.1. Study GS-98-437

The frequency of *confirmed* increases (defined as two consecutive laboratory measurements) in serum creatinine to ≥ 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL (grade 2 or higher) are presented in Table 3.2.1A. It should be noted that the two consecutive measurements were not necessarily performed within a short time after the first abnormal results. In many cases, the second measurement was obtained a month later at the next study visit. For comparison, the incidence of *any isolated* increase in serum creatinine to ≥ 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL in the first 48 weeks of this study is also presented in Table 3.2.1B. It is clear from these results that the majority of elevated serum creatinine values or hypophosphatemia were not replicated or confirmed by a subsequent measurement in patients receiving 10mg of adefovir. In general, the frequencies of the same laboratory abnormalities in the second 48 weeks of the study (which involved only adefovir 10 mg daily) were not significantly different from those seen in the adefovir 10 mg group in the first 48 weeks.

Table 3.2.1A. Incidence of Confirmed Increased Serum Creatinine to ≥ 0.3 mg/dL from Baseline and Hypophosphatemia to < 2.0 mg/dL in the First 48 Weeks of Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Creatinine increase to ≥ 0.3 mg/dL	69 (40%)	9 (5%)	1 (< 1%)
Resolved to ≤ 0.2 mg/dL[1]	42 (61%)	6 (67%)	0
Unresolved[2]	27 (39%)	3 (33%)	1 (100%)
Number remaining on full dose	31 (45%)	4 (44%)	1 (100%)
Number with dose reduction	38 (55%)	5 (56%)	0
Hypophosphatemia to < 2.0 mg/dL	9 (5%)	0	2 (1%)
Resolved to ≥ 2.0 mg/dL	9 (100%)	0	2 (100%)
On full dose	3 (33%)	0	2 (100%)
With dose reduction	4 (44%)	0	0
With dose interruption	2 (22%)	0	0
Requiring supplementation	6 (67%)	0	0

[1] By week 48 of study
[2] Unresolved to ≤ 0.2 mg/dL from baseline while remaining on full dose or with dose reduction.

Table 3.2.1B. Incidence of Any Increased Serum Creatinine to ≥ 0.3 mg/dL from Baseline and Hypophosphatemia < 2.0 mg/dL in the First 48 Weeks of Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Creatinine increase			
Grade 1 (1.5 to 2.0 mg/dL)	17 (10%)	2 (1%)	0
Grade 2 (2.1 to 3.0 mg/dL)	0	0	0
0.3 to < 0.5 mg/dL from baseline	63 (37%)	24 (14%)	14 (8%)
≥ 0.5 mg/dL from baseline	35 (20%)	2 (1%)	0
Hypophosphatemia			
Grade 1 (2.0 to 2.4 mg/dL)	15 (9%)	6 (4%)	8 (5%)
Grade 2 (1.5 to 1.9 mg/dL)	21 (12%)	4 (2%)	9 (5%)
Grade 3 (1.0 to 1.4 mg/dL)	5 (3%)	1 (< 1%)	0
Grade 4 (< 1.0 mg/dL)	1 (< 1%)	0	0

The proportion of males and females affected by either confirmed serum creatinine increase or confirmed hypophosphatemia or both were 81% and 19%, respectively. The racial distribution of patients with these abnormal laboratory parameters were 37% Caucasians, 58% Asians, and 5% others. These figures are comparable to the demographic composition of patients in this study.

3.2.2. Study GS-98-438

The frequency of *confirmed* increases in serum creatinine to ≥ 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL in the first 48 weeks of this study is summarized in Table 3.2.2. The incidence of serum creatinine increases in the adefovir 10 mg group was numerically less than the placebo group in this study and was also less than that observed in study GS-98-437.

Table 3.2.2. Incidence of Confirmed Increased Serum Creatinine to ≥ 0.3 mg/dL from Baseline and Hypophosphatemia < 2.0 mg/dL in the First 48 Weeks of Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Creatinine increase to ≥ 0.3 mg/dL	3 (2%)	3 (5%)
Resolved to ≤ 0.2 mg/dL[1]	2 (67%)	3 (100%)
Unresolved[2]	1	N/A
Number remaining on full dose	2	3
Number with dose reduction	1	0
Hypophosphatemia to < 2.0 mg/dL	0	0

[1] By week 48 of study
[2] Unresolved to ≤ 0.2 mg/dL from baseline while remaining on full dose or with dose reduction.

3.2.3. Time to Onset and Time to Resolution of Serum Creatinine Abnormality and Hypophosphatemia in Studies GS-98-437 and GS-98-438 (Integrated Summary)

Data on the time to confirmed increase in serum creatinine to ≥ 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL (grade 1) by Kaplan-Meier analysis for both studies GS-98-437 and GS-98-438 are summarized in Table 3.2.3A. Approximately half of the patients with serum creatinine increases to ≥ 0.3 mg/dL from baseline in the adefovir 30 mg group experienced the event by week 32 and those in the adefovir 10 mg group by week 28. The time to onset of hypophosphatemia (grade 1 or higher) in affected adefovir-treated patients (adefovir 30 mg group) was approximately 28 weeks. Data on the time to resolution of serum creatinine increase (to ≤ 0.2 mg/dL from baseline) and hypophosphatemia (to > 2.0 mg/dL) are summarized in Table 3.2.3B. Approximately 82% and 78% of patients (Kaplan-Meier estimate) in the adefovir 10 mg group and adefovir 30 mg group had resolution of serum creatinine increases by 16 weeks and 20 weeks, respectively, after onset. Virtually all patients with hypophosphatemia had resolution of the abnormality with or without oral supplementation within 16 weeks of onset.

Table 3.2.3A. Time to Confirmed Increase of Serum Creatinine to ≥ 0.3 mg/dL from Baseline and Hypophosphatemia to < 2.0 mg/dL in the First 48 Weeks in Study GS-98-437 and GS-98-438 (Integrated Summary)

	Treatment Group					
	ADV 30 mg (n = 173)		ADV 10 mg (n = 294)		Placebo (n = 228)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Creatinine increase						
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	0	0%	0	0%	0	0%
> Week 4 - week 8	2	1%	1	0%	0	0%
> Week 8 - week 12	2	1%	1	0%	0	0%
> Week 12 - week 16	2	1%	2	1%	2	1%
> Week 16 - week 20	6	4%	3	1%	2	1%
> Week 20 - week 24	12	7%	5	2%	4	2%
> Week 24 - week 28	18	11%	6	2%	4	2%
> Week 28 - week 32	31	19%	7	2%	4	2%
> Week 32 - week 36	47	28%	10	3%	4	2%
> Week 36 - week 40	56	34%	11	4%	4	2%
> Week 40 - week 44	61	37%	12	4%	4	2%
> Week 44 - week 48	69	42%	12	4%	4	2%
Hypophosphatemia						
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	0	0%	0	0%	0	0%
> Week 4 - week 8	0	0%	0	0%	0	0%
> Week 8 - week 12	0	0%	0	0%	1	0%
> Week 12 - week 16	0	0%	0	0%	1	0%
> Week 16 - week 20	0	0%	0	0%	1	0%
> Week 20 - week 24	1	1%	0	0%	1	0%
> Week 24 - week 28	4	2%	0	0%	2	1%
> Week 28 - week 32	9	5%	0	0%	2	1%
> Week 32 - week 36	9	5%	0	0%	2	1%
> Week 36 - week 40	9	5%	0	0%	2	1%
> Week 40 - week 44	9	5%	0	0%	2	1%
> Week 44 - week 48	9	5%	0	0%	2	1%

Table 3.2.3B. Time to Resolution of Increase of Serum Creatinine to ≤ 0.2 mg/dL from Baseline (Unconfirmed) and Hypophosphatemia to > 2.0 mg/dL (Unconfirmed) in the First 48 Weeks in Study GS-98-437 and GS-98-438 (Integrated Summary)

	Treatment Group					
	ADV 30 mg (n = 69)[1]		ADV 10 mg (n = 12)[1]		Placebo (n = 4)[1]	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Creatinine						
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	3	4%	0	0%	0	0%
> Week 4 - week 8	15	23%	0	0%	1	25%
> Week 8 - week 12	32	54%	6	52%	2	50%
> Week 12 - week 16	39	69%	8	82%	3	75%
> Week 16 - week 20	42	78%	8	82%	3	75%
> Week 20 - week 24	42	78%	8	82%	3	75%
> Week 24 - week 28	42	78%	8	82%	3	75%
> Week 28 - week 32	42	78%	8	82%	3	75%
> Week 32 - week 36	42	78%	8	82%	3	75%
> Week 36 - week 40	42	78%	8	82%	3	75%
> Week 40 - week 44	42	78%	8	82%	3	75%
> Week 44 - week 48	42	78%	8	82%	3	75%
Phosphorus						
Number of patients at risk		9				2
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	1	11%	0	0%	0	0%
> Week 4 - week 8	5	56%	0	0%	0	0%
> Week 8 - week 12	8	89%	0	0%	1	50%
> Week 12 - week 16	9	100%	0	0%	2	100%
> Week 16 - week 20	9	100%	0	0%	2	100%
> Week 20 - week 24	9	100%	0	0%	2	100%
> Week 24 - week 28	9	100%	0	0%	2	100%
> Week 28 - week 32	9	100%	0	0%	2	100%
> Week 32 - week 36	9	100%	0	0%	2	100%
> Week 36 - week 40	9	100%	0	0%	2	100%
> Week 40 - week 44	9	100%	0	0%	2	100%
> Week 44 - week 48	9	100%	0	0%	2	100%

[1] Number of patients at risk

3.2.4. Study GS-98-435

The evaluation of nephrotoxicity in this study is complicated by the underlying advanced disease status of the participants. Of those who experienced a significant increases in serum creatinine while receiving adefovir, many were also taking concomitant nephrotoxic drugs, particularly those in subcohort A (post-liver transplantation). A

significant proportion of patients in this study also had renal dysfunction at baseline as shown in Table 3.2.4A.

Table 3.2.4A. Baseline Serum Creatinine of Study GS-98-435

	Treatment Cohort[1]			
	1A (n = 117)	2A (n = 12)	3A (n = 62)	Total (n = 191)
Baseline serum creatinine				
Grade 1 (1.5 - 2.0 mg/dL)	17 (15%)	3 (25%)	11 (18%)	31 (16%)
Grade 2 (2.1 - 3.0 mg/dL)	2 (2%)	0	6 (10%)	8 (4%)
Grade 3 (3.1 - 6.0 mg/dL)	1 (< 1%)	0	2 (3%)	3 (2%)
Grade 4 (> 6.0 mg/dL)	0	0	0	0
Total	20 (17%)	3 (25%)	19 (31%)	42 (22%)
	1B (n = 46)	2B (n = 2)	3B (n = 80)	Total (n =128)
Baseline serum creatinine				
Grade 1	1 (2%)	0	3 (37%)	8 (6%)
Grade 2	0	0	0	0
Grade 3	0	0	1 (1%)	2 (2%)
Grade 4	0	0	2 (2%)	4 (3%)
Total	1 (2%)	0	6 (7%)	14 (11%)

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort A: post-liver transplantation patients; Subcohort B: patients waitlisted for a liver transplant.

The frequency of *any* increase in serum creatinine and hypophosphatemia is summarized in Table 3.2.4B. At the time this briefing document was prepared, the frequency of *confirmed* changes has not been completely analyzed. We will present updated data on August 6, 2002.

Table 3.2.4B. Incidence of Any Increased Serum Creatinine to ≥ 0.3 mg/dL from Baseline and Hypophosphatemia to < 2.0 mg/dL of Study GS-98-435 (as of Safety Update Cutoff Date)

	Treatment Cohort[1]			
	1A (n = 117)	2A (n = 12)	3A (n = 62)	Total (n = 191)
Creatinine increased				
Grade 1 (1.5 - 2.0 mg/dL)	30 (29%)	6 (55%)	18 (32%)	54 (32%)
Grade 2 (2.1 - 3.0 mg/dL)	13 (13%)	1 (9%)	12 (21%)	26 (15%)
Grade 3 (3.1 - 6.0 mg/dL)	1 (1%)	0	4 (7%)	5 (3%)
Grade 4 (> 6.0 mg/dL)	3 (3%)	0	1 (2%)	4 (2%)
0.3 to < 0.5 mg/dL[1]	22 (22%)	2 (18%)	7 (13%)	31 (18%)
≥ 0.5 mg/dL[1]	24 (24%)	3 (27%)	17 (30%)	44 (26%)
Hypophosphatemia				
Grade 1 (2.0-2.4 mg/dL)	10 (10%)	4 (36%)	5 (9%)	19 (11%)
Grade 2 (1.5-1.9 mg/dL)	5 (5%)	1 (9%)	0	6 (4%)
Grade 3 (1.0-1.4 mg/dL)	0	0	1 (2%)	1 (1%)
Grade 4 (< 1.0 mg/dL)	0	0	0	0
	1B (n = 42)	2B (n = 2)	3B (n = 59)	Total (n =103)
Creatinine increased				
Grade 1	2 (5%)	0	6 (10%)	8 (6%)
Grade 2	1 (2%)	0	5 (8%)	0
Grade 3	2 (5%)	0	3 (5%)	2 (2%)
Grade 4	0	0	1 (2%)	4 (3%)
0.3 to < 0.5 mg/dL[2]	4 (10%)	0	3 (5%)	7 (7%)
≥ 0.5 mg/dL[2]	7 (17%)	0	12 (20%)	19 (18%)
Hypophosphatemia				
Grade 1	2 (5%)	0	5 (8%)	7 (7%)
Grade 2	2 (5%)	1 (50%)	4 (7%)	7 (7%)
Grade 3	1 (2%)	0	1 (2%)	2 (2%)
Grade 4	0	0	0	0

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort A: post-liver transplantation patients; Subcohort B: patients waitlisted for a liver transplant.
[2] Change from baseline

It is informative to review the shift in grade of serum creatinine from baseline during the study. Results of grade shift in cohorts 1A, 2A, and 3A (post-liver transplantation) are summarized in Table 3.2.4C, and those in cohorts 1B, 2B, and 3B (waitlisted for liver transplantation) in Table 3.2.4D. Most affected patients in subcohort A experienced a shift from normal at baseline to grade 1, or from grade 1 at baseline to grade 2 during the study. Most affected patients in subcohort B had a shift from normal at baseline to grade 2.

Table 3.2.4C. Shift in Post-Baseline Serum Creatinine Toxicity Grade in Subcohort A (Post-Liver Transplantation) of Study GS-98-435

Shift in Serum Creatinine	Treatment Cohort[1]			
	1A (n = 117)	2A (n = 12)	3A (n = 62)	Total (n = 191)
Normal at baseline, n	77	6	33	116
Shift during treatment to:				
Normal	51 (66%)	4 (67%)	20 (61%)	75 (65%)
Grade 1	21 (27%)	2 (33%)	8 (24%)	31 (27%)
Grade 2	3 (4%)	0	4 (12%)	7 (6%)
Grade 3	0	0	1 (3%)	1 (1%)
Grade 4	2 (3%)	0	0	2 (2%)
Grade 1 at baseline, n	17	3	11	31
Shift during treatment to:				
Normal	2 (12%)	0	0	2 (6%)
Grade 1	8 (47%)	2 (67%)	8 (73%)	18 (58%)
Grade 2	6 (35%)	1 (33%)	3 (27%)	10 (32%)
Grade 3	1 (6%)	0	0	1 (3%)
Grade 4	0	0	0	0
Grade 2 at baseline, n	2	0	6	8
Shift during treatment to:				
Normal	0	0	0	0
Grade 1	0	0	1 (17%)	1 (13%)
Grade 2	2 (100%)	0	4 (67%)	6 (75%)
Grade 3	0	0	1 (17%)	1 (13%)
Grade 4	0	0	0	0
Grade 3 at baseline, n	1	0	2	3
Shift during treatment to:				
Normal	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	2 (100%)	2 (67%)
Grade 4	1 (100%)	0	0	1(33%)
Grade 4 at baseline, n	0	0	0	0

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort A: post-liver transplantation patients

Table 3.2.4D. Shift in Post-Baseline Serum Creatinine Toxicity Grade in Subcohort B (Waitlisted for Liver Transplantation) of Study GS-98-435

Shift in Serum Creatinine	Treatment Cohort[1]			
	1B (n = 46)	2B (n = 2)	3B (n = 80)	Total (n = 128)
Normal at baseline, n	41	2	58	116
Shift during treatment to:				
	37 (90%)	2 (100%)	45 (78%)	84 (83%)
Normal	2 (5%)	0	6 (10%)	8 (8%)
Grade 1	1 (2%)	0	5 (9%)	6 (6%)
Grade 2	1 (2%)	0	2 (3%)	3 (3%)
Grade 3	0	0	0	0
Grade 4				
	1	0	3	4
Grade 1 at baseline, n				
Shift during treatment to:	0	0	2 (67%)	2 (50%)
Normal	0	0	1 (33%)	1 (25%)
Grade 1	0	0	0	0
Grade 2	1 (100%)	0	0	1 (25%)
Grade 3	0	0	0	0
Grade 4				
	0	0	0	0
Grade 2 at baseline, n				
	0	0	1	1
Grade 3 at baseline, n				
Shift during treatment to:	0	0	0	0
Normal	0	0	0	0
Grade 1	0	0	1 (100%)	1 (100%)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4				
	0	0	2	2
Grade 4 at baseline, n				
Shift during treatment to:	0	0	0	0
Normal	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	1 (50%)	1 (50%)
Grade 3	0	0	1 (50%)	1 (50%)
Grade 4				

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort B: patients waitlisted for a liver transplant.

Data on the time to a confirmed increase (defined as two consecutive measurements) in serum creatinine to ≥ 0.5 mg/dL from baseline (*not* ≥ 0.3 mg/dL from baseline as in studies GS-98-437 and GS-98-438 due to the relatively higher number of patients with baseline renal impairment in this study) by Kaplan-Meier analysis for subcohort A (post-liver transplantation) of this study are summarized in Table 3.2.4E.

Table 3.2.4E. Time to Confirmed Increase of Serum Creatinine to ≥ 0.5 mg/dL from Baseline in Subcohort A (Post-Liver Transplantation) of Study GS-98-435

	Treatment Cohort[1]					
	1A (n = 117)		2A (n = 12)		3A (n = 67)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Baseline	0	0	0	0	0	0
> Baseline - week 4	0	0	0	0	0	0
> Week 4 - week 8	0	0	0	0	1	2
> Week 8 - week 12	3	3	0	0	1	2
> Week 12 - week 16	3	3	0	0	1	2
> Week 16 - week 20	3	3	0	0	3	7
> Week 20 - week 24	4	4	0	0	3	7
> Week 24 - week 28	5	5	0	0	3	7
> Week 28 - week 32	7	8	0	0	4	9
> Week 32 - week 36	7	8	0	0	5	12
> Week 36 - week 40	9	11	0	0	6	15
> Week 40 - week 44	10	12	0	0	6	15
> Week 44 - week 48	10	12	0	0	6	15
> Week 48 - week 52	10	12	0	0	6	15
> Week 52 - week 56	10	12	0	0	6	15
> Week 56 - week 60	10	12	0	0	6	15
> Week 60 - week 64	11	14	0	0	6	15
> Week 64 - week 68	12	16	1	13	6	15
> Week 68 - week 72	12	16	1	13	6	15
> Week 72 - week 76	14	21	1	13	6	15
> Week 76 - week 80	14	21	1	13	6	15
> Week 80 - week 84	15	24	1	13	6	15
> Week 84 - week 88	17	30	1	13	7	22
> Week 88 - week 92	17	30	1	13	7	22
> Week 92 - week 96	18	33	1	13	7	22

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort A: post-liver transplantation patients; Subcohort B: patients waitlisted for a liver transplant.

Similarly, data on the time to confirmed increase in serum creatinine to ≥ 0.5 mg/dL from baseline by Kaplan-Meier analysis for subcohort B (waitlisted for liver transplantation) are summarized in Table 3.2.4F. By week 96 of the study, 17 patients (56% by K-M estimate) in subcohort B, 5 (26%) in cohort 1B, none in cohort 2B, and 10 (30%) in cohort 3B, developed a serum creatinine increases to ≥ 0.5 mg/dL above the baseline.

Table 3.2.4F. Time to Confirmed Increase of Serum Creatinine to ≥ 0.5 mg/dL from Baseline in Subcohort B (Waitlisted for Liver Transplantation) of Study GS-98-435

	Treatment Cohort[1]					
	1B (n = 46)		2B (n = 2)		3B (n = 80)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Baseline	0	0	0	0	0	0
> Baseline - week 4	0	0	0	0	0	0
> Week 4 - week 8	0	0	0	0	2	3
> Week 8 - week 12	1	2	0	0	2	3
> Week 12 - week 16	2	5	0	0	5	10
> Week 16 - week 20	3	9	0	0	7	16
> Week 20 - week 24	4	13	0	0	7	16
> Week 24 - week 28	4	13	0	0	8	19
> Week 28 - week 32	4	13	0	0	8	19
> Week 32 - week 36	4	13	0	0	9	24
> Week 36 - week 40	4	13	0	0	9	24
> Week 40 - week 44	4	26	0	0	10	30
> Week 44 - week 48	5	26	0	0	10	30
> Week 48 - week 52	5	26	0	0	10	30
> Week 52 - week 56	5	26	0	0	10	30
> Week 56 - week 60	5	26	0	0	10	30
> Week 60 - week 64	5	26	0	0	10	30
> Week 64 - week 68	5	26	0	0	10	30
> Week 68 - week 72	5	26	0	0	10	30
> Week 72 - week 76	5	26	0	0	10	30
> Week 76 - week 80	5	26	0	0	10	30
> Week 80 - week 84	5	26	0	0	10	30
> Week 84 - week 88	5	26	0	0	10	30
> Week 88 - week 92	5	26	0	0	10	30
> Week 92 - week 96	5	26	0	0	10	30

[1] Cohort 1: adequate renal, hepatic, and hematologic function at baseline; Cohort 2: patients from study GS-99-451i; Cohort 3: inadequate renal, hepatic, hematologic, and other condition at baseline; Subcohort A: post-liver transplantation patients; Subcohort B: patients waitlisted for a liver transplant.

By week 96 of study 435, 26 patients (68% by K-M estimate) in subcohort A developed serum creatinine increase to ≥ 0.5 mg/dL above the baseline. Of these, 18 patients (33%) were in cohort 1A, one (13%) in cohort 2A, and seven (22%) in cohort 3A. Of note is that the proportion is higher in cohort 1A (33% by K-M estimate), i.e., patients with adequate renal, hepatic, and hematologic function, than in cohort 3A (22% by K-M estimate), i.e., patients with inadequate renal, hepatic, and hematologic function.

Of the 26 patients in subcohort A who experienced serum creatinine increase to ≥ 0.5 mg/dL above the baseline at week 96, 21 patients (84%) had creatinine clearance of less than 80 mL/min (indicative of some degree of renal impairment), and 11 patients (44%) had grade 1 or higher (≥ 1.5 mg/dL) baseline serum creatinine. All of these patients (100%) were also taking concomitant immunosuppressants (58% on cyclosporine, 42%

on tacrolimus). Of the 15 patients in subcohort B with serum creatinine increase to ≥ 0.5 mg/dL above the baseline at week 96, 6 patients (40%) had creatinine clearance less than 80 mL/min, and one patient (7%) had baseline serum creatinine grade 1 or higher.

Narrative reports on a number of patient reports of treatment-emergent nephrotoxicity are presented in detail in Appendix B. For some, the association between adefovir treatment and nephrotoxicity appears to be temporally related.

4. Conclusion on the Potential Role of Adefovir in Treatment-Emergent Nephrotoxicity

Based on information from studies GS-98-437 and GS-98-438 (which enrolled patients with compensated liver disease with adequate renal function), it appears that the clinical benefit of adefovir 10 mg is substantial and the nephrotoxicity risk is low, but perhaps not zero. However, in study GS-98-435, the proportion of patients who developed treatment-emergent nephrotoxicity was substantially higher than that observed in studies GS-98-437 and GS-98-438. Case-by-case analysis suggests that adefovir may have been a contributing factor to these patients' worsening renal status. We recognize that multiple confounding factors including advanced disease state, underlying renal insufficiency, and the concurrent use of known nephrotoxic drugs were present in these cases. The totality of evidence, however, raises some caution regarding the use of adefovir in patients with significant pre-existing renal function impairment. Therefore, we will be seeking the Committee's comments on the safety of adefovir in chronic hepatitis B patients with decompensated disease and/or pre-existing renal impairment. Recommendations for additional studies or analyses on this issue will be solicited from the Committee.

To address the treatment-emergent nephrotoxicity issue, we are aware that the applicant is in the process of finalizing a clinical study protocol to evaluate the safety of adefovir in chronic hepatitis B patients with renal dysfunction using the following dosing guideline:

Creatinine Clearance (mL/min)					Requiring Hemodialysis
> 80	50-80	20-49	10-19	< 10	
Adefovir 10 mg once daily		Adefovir 10 mg every 48 hours	Adefovir 10 mg every 72 hours	Adefovir 10 mg every 7 days	Adefovir 10 mg every 7 days post hemodialysis

The proposed dose interval modifications are based on results of the adefovir pharmacokinetic study GS-00-473 in patients with varying degree of renal insufficiency as determined by the creatinine clearance.

5. Resistance Issues

Although studies of HBV resistance to adefovir and studies evaluating treatment responses to adefovir in lamivudine-resistant HBV are ongoing, we note the following observations:

- The development of resistance to adefovir in patients chronically infected with HBV has not been observed. In studies GS-98-437 (HBeAg-positive patients) and GS-98-438 (HBeAg-negative patients), no mutations associated with treatment failure were observed up to 48 weeks of therapy.

- Cross-resistance to adefovir was not observed in lamivudine-resistant HBV. In ongoing studies in patients with lamivudine resistant HBV, HBV-DNA reductions over 24 weeks appear to be comparable to that observed in studies of treatment naive individuals (studies GS-98-437 and GS-98-438).

    - The proposed dose for HBV is less than the effective concentrations against HIV. Thus, there is some concern that treatment of co-infected individuals will select for HIV harboring the K65R mutation conferring reduced susceptibility to adefovir. This mutation shows cross-resistance to ddI, ddC, abacavir, and tenofovir.

6. Pediatric Drug Development

In a clinical development meeting on April 25, 2000, we requested that the applicant submit a pediatric drug development plan at the earliest possible time. The applicant subsequently submitted the Proposed Pediatric Study Request on September 28, 2001, to IND 52,182. We issued a Written Request on April 12, 2002, for the following studies:

- Study(ies) to determine the pharmacokinetic profile of multiple dose levels of adefovir dipivoxil in pediatric patients with chronic hepatitis B from 2 to 17 years of age.

- Randomized, placebo-controlled study(ies), 48 to 96 weeks in duration, to determine safety and effectiveness of adefovir dipivoxil in pediatric population with chronic hepatitis B.

To our knowledge, the applicant plans to initiate clinical studies of adefovir in chronic hepatitis B pediatric patients in the second quarter of 2002.

7. Issues for Discussion

At present, we have tentatively identified the following issues that we would like to ask the Committee to address during the discussion period:

7.1. Efficacy Issues

We would like the Committee to comment on the strength of the efficacy data of adefovir 10 mg for the treatment of chronic hepatitis B patients with the following characteristics: compensated liver disease, decompensated liver disease, lamivudine-resistant hepatitis B virus, presumed pre-core mutant disease, and co-infection with HBV and HIV.

7.2. Safety Issues

We would like the Committee to comment on the safety of adefovir 10 mg daily in chronic hepatitis B patients, specifically those with baseline renal insufficiency and/or decompensated liver disease.

7.3. Resistance Issues

We would like the Committee to comment on the following resistance issues related to the drug:

- The strength of the virology data assessing the emergence of HBV resistance to adefovir.
- The use of adefovir treatment in patient population with lamivudine-resistant hepatitis B virus.
- The recommendations for special precautions when treating HIV/HBV co-infected patients with adefovir 10 mg daily.

7.4. Recommendations for Post Marketing Studies:

We would appreciate any recommendations from the Committee on post-marketing studies. Demographic data of study GS-98-437 (the "pivotal" study with US study sites) indicated that African American, Hispanic American, and American Indian and Alaskan Native patients with chronic hepatitis B were significantly underrepresented in the applicant's drug development program. While there is no evidence to date to suggest that these patients respond differently to adefovir treatment, we believe that the applicant should make an attempt to enroll these patients in any ongoing and future clinical studies of adefovir. We would like the Committee to comment on the types of studies/analyses that should be conducted to provide more information on the safety and efficacy of adefovir in under-represented patient subgroups including demographic subgroups (race, pediatrics) and subgroups defined by baseline disease characteristics.

We realize that additional issues may emerge prior to the meeting. In such cases, we will attempt to provide the Committee with background information and the subjects to be discussed.

Appendix A

Selected Cases of Deaths Reported in Study GS-98-435

It should be noted that a number of confounding factors (e.g., concomitant use of nephrotoxic drug, underlying advanced medical condition) were present in each of the following cases. However, in light of the pharmacokinetics of adefovir in renally impaired patients presented under section 3 in the briefing document, there are reasons for concern that adefovir even at a dose of 10 mg daily could have played a contributory role in the renal event in these patients, particularly in those with pre-existing renal function impairment. The acute renal failure in two patients resulted in hemodialysis.

- A 65-year-old white male status post liver transplant on December 5, 1991, started adefovir 10 mg daily on November 1, 1999. Baseline laboratory results were: ALT 408 U/L; total bilirubin 1.7 mg/dL; albumin 2.8 g/L; creatinine 1.9 mg/dL; calculated creatinine clearance 40.3 mL/min; phosphorus 2.3 mg/dL; HBV DNA 7.03 $\log_{10}$ copies/mL; and Child-Pugh score 6. Concomitant medications included cyclosporine, sirolimus, co-trimoxazole, and furosemide.

  Relevant laboratory test results were as follows:

Date:	11/99	01/00	03/00	04/00	08/00	11/00	12/00
Creatinine:	1.9	2.5	3.0	2.9	3.1	4.7	6.1
Cr. Cl.:	40.3	29.9	25.2	26.1	24.6	25.3	2.6

  On May 23, 2000, adefovir dose was reduced to 5 mg daily due to serum creatinine increase to 3.0 mg/dL. Following dose reduction, serum HBV DNA levels continued to be suppressed. In July 2000, serum HBV DNA was 2.60 $\log_{10}$ copies/mL. On November 27, 2000, the patient was hospitalized with confusion. Laboratory testing showed ALT 229 U/L, AST 418 U/L, PT 15.7 seconds, plasma ammonia 48 µg/dL (?) (Reference range: 15-50 µg/dL). His mental status improved with treatment. A liver biopsy showed moderate chronic hepatitis and superimposed acute rejection. On December 2, 2000, laboratory testing revealed creatinine of 6.4 mg/dL. Eleven days later, the patient began dialysis for renal failure. Adefovir dosing was reduced to 5 mg every other day. On December 28, 2000, he developed respiratory arrest and expired.

- A 58-year-old white male status post liver transplant on August 9, 1998, started adefovir 10 mg daily on August 10, 2000. Baseline laboratory results were: ALT 164 U/L; total bilirubin 1.9 mg/dL; albumin 3.4 g/dL; BUN 47 mg/dL; creatinine 1.2 mg/dL; and calculated creatinine clearance 66.3 mL/min. Concomitant medications included lamivudine, tacrolimus, clonidine, prednisone, famotidine, and furosemide. On September 1, 2000, the patient was started on furosemide for pedal edema. Five days later, he was hospitalized for abdominal pain, nausea, vomiting, and diarrhea, dehydration, and found to have serum tacrolimus level of 41.6 µg/L (target therapeutic level: 5-15 µg/L). Tacrolimus was temporarily discontinued. Laboratory

tests on September 5, 2000, revealed creatinine 3.1 mg/dL, BUN 73 mg/dL, ALT 233 U/L, total bilirubin 5.5 mg/dL, albumin 2.6 g/dL, and creatinine clearance of 28.0 mL/min. On September 13, 2000, adefovir was reduced to 5 mg daily. The patient was found unresponsive the next day and subsequently expired on September 15, 2000. Autopsy revealed recurrent necrotizing hepatitis and probable ischemic colitis. The investigator assessed the event as possibly related to adefovir and death due to underlying liver disease.

- A 62-year-old male started adefovir 10 mg daily on March 27, 2001. Baseline laboratory results were: ALT 219 U/L; total bilirubin 36.0 mg/dL; albumin 3.7 g/L; creatinine 1.6 mg/dL; PT 21.2 seconds; calculated creatinine clearance 68.6 mL/min; phosphorus 2.8 mg/dL; HBV DNA 7.07 $\log_{10}$ copies/mL; and Child-Pugh score 10. Concomitant medications included lamivudine, rifaximin, lactulose, dopamine, omeprazole, ursedeoxycholic acid, and doxazosin. On March 31, 2001, the patient had clinical signs of hepatic encephalopathy. Laboratory tests were noted for serum creatinine of 2.2 mg/dL, BUN of 79 mg/dL, ALT of 198 U/L, and total bilirubin of 37.8 mg/dL. On April 1, 2001, the patient became anuric with creatinine peaked at 4.6 mg/dL. Adefovir was discontinued. A consulting nephrologist suggested that an acute toxic insult might have led to acute renal failure. The investigator assessed that adefovir was a possible/probable causal factor due to the temporal relationship. The patient subsequently suffered a cardiopulmonary arrest later that day and died the next day.

- A 43-year-old white male on the waiting list for liver transplant started adefovir 10 mg daily on October 17, 2000. Baseline laboratory results were: ALT 171 U/L; total bilirubin 5.1 mg/dL; albumin 1.8 g/L; creatinine 0.7 mg/dL; and calculated creatinine clearance 144.3 mL/min. Significant medical history included myalgia, leg cramps, and elevated creatine kinase (270 U/L on October 16, 2001). Laboratory testing on October 19, 2000, showed creatine kinase 484 U/L, and myoglobin 90 μg/mL. Adefovir was interrupted. By October 22, 2000, creatine kinase values had returned to normal and adefovir was restarted the next day. After restating the study drug, the leg cramps increased in intensity. Adefovir was once again interrupted. On November 20, 2000, adefovir was restarted. On December 1, 2000, the patient had an acute episode of esophageal hemorrhage requiring vasopressors, fresh frozen plasma, platelets, and coagulant factor infusion. He apparently developed metabolic acidosis, acute renal failure, and anuria. Dialysis was started. On December 2, 2000, he had liver transplantation surgery and was started on cyclosporine and basiliximab. Adefovir dosing was changed to 10 mg three times weekly. His hospital course was stormy with sepsis, fever of unknown origin, pleural effusion, cholestasis, epistaxis, cytomegalovirus and herpes simplex virus infection. Laboratory testing on January 11, 2001 revealed serum creatinine of 4.7 g/dL. His last dialysis was on January 25, 2001. He was discharged from the hospital on February 8, 2001 with serum creatinine of 3.6 mg/dL. On April 9, 2002, serum creatinine was 2.8 mg/dL.

- A 40-year-old male started adefovir 10 mg daily on January 20, 2001. Baseline laboratory results were: ALT 106 U/L; total bilirubin 26.7 mg/dL; albumin 2.0 g/L;

creatinine 0.87 mg/dL; PT 23.6 seconds; and HBV DNA 390 pg/mL. Concomitant medications included lamivudine, propoxyphene, and levofloxacin. Prior to adefovir therapy, his creatinine levels were between 0.6-1.2 mg/dL.

Relevant laboratory test results were as follows:

Date:	01/17	01/19	01/20	01/21	01/30	02/20	02/24	02/25
Creatinine:	0.87	0.98	1.01	1.03	1.21	1.86	4.04	5.09
Bilirubin:	11.3	26.7	45.9	45.9	21.3	45.9	52.6	50.9

On February 21, 2001, adefovir dose was reduced to 5 mg daily. The patient was thought to develop hepatorenal syndrome and expired on February 26, 2001. The investigator could not rule out study drug as a possible contributory factor to the patient's demise.

- A 42-year-old white male who was co-infected with HIV and lamivudine-resistant HBV previously received adefovir for HIV from November 23, 1999 (baseline serum creatinine 0.9 mg/dL) to October 3, 2001. Serum creatinine on October 30, 2001 was 1.2 mg/dL. On January 21, 2002, his screening serum creatinine was 1.4 mg/dL. The patient was reportedly hospitalized the next day with reactivation of hepatitis B disease, hepatorenal syndrome, HIV, abdominal pain, and mental status changes. On January 25, 2002, adefovir 5 mg daily was started with baseline serum creatinine 2.6 mg/dL, ALT 265 U/L, AST 705 U/L, total bilirubin 25.5 mg/dL, albumin 2.8 g/dL, and PT 38.7 seconds. On January 30, 2002, serum creatinine increased to 5.5 mg/dL. On January 31, 2002, serum creatinine reached 6.2 mg/dL, BUN 78 mEq/L, and total bilirubin 51.3 mg/dL. The patient expired the next day. The investigator assessed the event as unrelated to adefovir.

Appendix B

Selected Cases of Renal Toxicity Reported in Study GS-98-435

Again, it should be stated that a number of confounding factors (e.g., concomitant use of nephrotoxic drug, underlying advanced medical condition) were present in all of the following cases. Nevertheless, in light of the pharmacokinetics of adefovir in renally impaired patients, there are reasons for concern that adefovir even at a dose of 10 mg daily could have played a contributory role in the renal event in most of these patients, particularly in those with pre-existing renal function impairment.

- A 68-year-old white male status post liver transplant on September 7, 1992, started adefovir 5 mg daily due to pre-existing renal dysfunction on May 25, 2000. Baseline laboratory results were: ALT 109 U/L; total bilirubin 1.4 mg/dL; albumin 3.7 g/dL; creatinine 1.3 mg/dL; creatinine clearance 57.7 mL/min; and phosphorus 3.1 mg/dL. Concomitant medications included cyclosporine, lorazepam, and paracetamol.

  The patient's relevant laboratory test results are summarized below:

Date:	05/00	08/00	11/00	01/01	04/01	08/01	09/01	10/01
Creatinine:	1.3	1.7	3.5	2.1	1.6	2.7	3.1	2.7
Phosphorus:	3.1	3.7	1.5	1.5	1.7	1.6	1.8	2.1
Proteinuria:	1+	1+	2+	2+	2+	2+	3+	2+

  On July 19, 2000, the adefovir dose was increased to 10 mg daily due to a decrease in serum creatinine to 1.2 mg/dL. On October 11, 2000, the dose was reduced to 5 mg daily due to increased serum creatinine to 2.0 mg/dL and serum phosphorus decreased to 1.5 mg/dL. Phosphate supplementation was initiated. On November 25, 2000, the patient was hospitalized with renal failure (peak serum creatinine 3.5 mg/dL). Adefovir was interrupted. The investigator attributed the renal failure to cyclosporine or adefovir. It is unclear whether adefovir was restarted. However, based on subsequent laboratory test results, it appears that the patient also suffered another episode of acute renal failure in September 2001.

- A 57-year-old white male status post liver transplant on February 20, 1991, started adefovir 5 mg daily on December 13, 1999. The reduced adefovir dose was due to his history of chronic renal insufficiency. Baseline laboratory results were: ALT 73 U/L; total bilirubin 0.2 mg/dL; albumin 3.8 g/dL; creatinine 2.2 mg/dL; creatinine clearance 40.4 mL/min; and phosphorus 2.6 mg/dL. Concomitant medications included lamivudine, tacrolimus, benazepril, diltiazem, trimethropin/sulfamethoxazole, omeprazole, aspirin and propxyphene/acetaminophen.

Relevant laboratory test results are summarized below:

Date:	12/99	06/00	09/00	04/01	05/01	06/01	09/01	01/02
Creatinine:	2.2	2.7	2.7	2.9	4.9	2.6	3.0	3.8
Cr. Cl.:	40.4	32.2	33.3	30.3	18.0	34.2	30.7	24.8

On May 21, 2001, the patient was hospitalized with a serum creatinine increase that peaked at 5.7 mg/dL (grade 3). Adefovir was interrupted. The next day, serum creatinine was 4.9 mg/dL, BUN 57 mg/dL, and phosphorus 6.1 mg/dL. The consulting nephrologist determined that the event was likely due to pre-renal azotemia superimposed on chronic renal insufficiency. Final diagnosis was acute renal failure on chronic renal insufficiency at the time of discharge on May 23, 2001. On June 4, 2001, adefovir 5 mg daily was restarted. According to the investigator, "the role of the patient's concomitant medications, including adefovir dipivoxil, could not be completely excluded, although unlikely."

- A 60-year-old man status post liver transplantation 7.5 years ago started adefovir 5 mg daily. Baseline laboratory results were: ALT 112 U/L; total bilirubin 0.2 mg/dL; albumin 3.3 g/dL; creatinine 3.1 mg/dL; and creatinine clearance 32.0 mL/min. Concomitant medications included lamivudine, tacrolimus, and antihypertensive agents.

  Relevant laboratory test results were as follows:

Date:	05/00	06/00	08/00	11/00	03/01	05/01	02/02
Creatinine:	3.1	4.2	4.3	5.5	4.8	4.2	4.2
Cr. Cl.:	32.0	21.3	20.8	16.0	19.1	22.0	20.9
Phosphorus:	6.0	6.0	5.0	5.0	4.9	5.1	4.2

  At week 4 (June 2000) of adefovir treatment, serum creatinine increased to 4.2 mg/dL, and by week 24 (November 2000), it peaked at 5.5 mg/dL (creatinine clearance of 16.0 mL/min). Throughout the entire time, adefovir dose was not adjusted. The investigator considered the event nonserious and possibly related to adefovir.

- A 42-year-old white male status post liver transplant on January 20, 2994, started adefovir 10 mg daily on August 14, 2000. Baseline laboratory results were: ALT 124 U/L; total bilirubin 5.6 mg/dL; albumin 2.9 g/dL; creatinine 1.4 mg/dL; and creatinine clearance 63.2 mL/min. According to the record, baseline creatinine levels were between 1.5-2.1 mg/dL over the last five years. Concomitant medications included tacrolimus, mycophenolate mofetil, calcitriol, omeprazole, ornithine aspartate, ursodiol, sodium fluoride, and Serafem.

Subsequent laboratory test results are shown below:

Date:	08/00	10/00	11/00	12/00	01/00	03/01
Creatinine:	1.3	1.9	4.2	7.3	4.2	2.8
Cr. Cl.:	63.2	46.6	34.6	?	20.4	29.7

On November 15, 2000, serum creatinine increased to 3.3 mg/dL. On November 21, 2000, the adefovir dose was reduced to 5 mg daily. On November 24, 2000, serum creatinine was 4.2 mg/dL. Adefovir was interrupted on December 5, 2000. The patient was hospitalized on December 6, 2000, for acute renal failure. Tacrolimus dose was reduced to 1 mg/day to maintain therapeutic levels. Hemodialysis three times weekly began from December 8, 2000 until January 1, 2001. A liver biopsy revealed chronic graft rejection. On January 2, 2001, serum creatinine decreased to 3.6 mg/dL. On January 9, 2001, adefovir 5 mg every other day was restarted. On January 10, 2001, creatinine again increased to 4.3 mg/dL. The adefovir dose was increased to 5 mg daily on January 14, 2001. On January 18, 2001, serum creatinine decreased to 3.8 mg/dL. The investigator assessed the event as possibly related to adefovir. The applicant concluded that "[w]hile a relationship to adefovir cannot be completely excluded in this case, other risk factors are more likely to be contributory to the event." Incidentally, on April 11, 2001, serum creatinine again increased to 7.7 with a creatinine clearance of 10.8 mL/min. There is no further record on this event.

- A 69-year-old man status post liver transplantation seven days prior to starting adefovir 10 mg daily in November 1999. Baseline laboratory results were: ALT 111 U/L; total bilirubin 1.7 mg/dL; albumin 3.1 g/dL; creatinine 0.9 mg/dL; and creatinine clearance 123.4 mL/min. Concomitant medications included lamivudine, tacrolimus, hepatitis B immune globulin, glyburide, and insulin. Relevant laboratory test results are as follows:

Date:	11/99	01/00	03/00	05/00	06/00	10/00	02/01
Creatinine:	0.9	1.6	1.4	2.0	1.9	1.5	1.5
Cr. Cl.:	123.4	58.4	62.3	46.7	49.7	63.8	64.7
Phosphorus:	2.0	4.8	3.5	2.9	2.8	3.1	3.2

At week 8 (January 2000), serum creatinine increased to 1.6 mg/dL. By week 24 (May 2000), serum creatinine was 2.0 mg/dL and adefovir was temporarily interrupted and restarted at a reduced dose of 5 mg daily. At week 28 (June 2000), serum creatinine decreased to 1.9 mg/dL and 1.5 mg/dL by week 44 (October 2000). The event was not reported as an adverse event by the investigator.

- A 69-year-old man status post liver transplantation 4.7 years ago started adefovir 10 mg daily. Baseline laboratory results were: ALT 57 U/L; total bilirubin 19.4 mg/dL; albumin 2.0 g/dL; creatinine 1.5 mg/dL; and creatinine clearance 51.0 mL/min. Concomitant medications included lamivudine, cyclosporine, and nifedipine. Relevant laboratory test results are as follows:

Date:	04/00	12/00	01/01	02/01	06/01	08/01	01/02
Creatinine:	1.5	1.8	2.0	2.1	2.1	2.2	2.2
Cr. Cl.:	51.0	40.8	37.8	34.9	37.3	36.4	37.6
Phosphorus:	2.6	3.1	2.4	1.8	2.6	2.8	3.0

Adefovir treatment was not interrupted until week 72 (August 2001) and then restarted at a reduced dose of 5 mg daily. The event was not reported as an adverse event by the investigator.

- A 60-year-old man was on dialysis while being waitlisted for liver transplantation. He started adefovir 10 mg after each dialysis. At baseline, serum creatinine was 6.2 mg/dL, creatinine clearance 13.5 mL/min., and serum HBV DNA 8.2 $\log_{10}$ copies/mL. Concomitant medications included lamivudine, furosemide and aldactone for ascites, and insulin for diabetes. By week 4, serum HBV DNA decreased to 6.1 $\log_{10}$ copies/mL. Other relevant laboratory test results include:

Date:	09/01	10/01	11/01	12/01	01/02	02/02
Creatinine:	6.2	9.5	8.5	8.5	7.7	8.9
Cr. Cl.:	13.5	9.0	10.1	10.1	11.1	9.6
Phosphorus:	3.8	5.6	3.8	3.5	2.7	3.4

- A 48-year-old Fijian Indian male on waiting list for liver transplantation started adefovir 10 mg daily on September 23 2000. Significant past medical history included renal transplant in 1982, hypertension, and diabetes. Baseline laboratory results were: ALT 190 U/L; total bilirubin 15.7 mg/dL; albumin 2.0 g/dL; creatinine 1.0 mg/dL; creatinine clearance 106.1 mL/min; and phosphorus 1.6 mg/dL. Concomitant medications included lamivudine, azathioprine, prednisolone, amlodipine, omeprazole, metoclopramide, and prochlorperazine. On October 7, 2000, laboratory testing showed serum creatinine of 1.3 mg/dL. On October 9, 2000, it increased to 1.9 mg/dL and further increased to 2.9 mg/dL the next day (creatinine clearance 36.5 mL/min). Adefovir was discontinued on October 9, 2000, and the patient was discontinued from the study on October 10, 2000. The investigator determined that the renal failure was due to progressive liver failure.

- A 50-year-old Asian female status post two liver transplants in 1992 and 1996 started adefovir 10 mg daily on August 19,1999. Baseline laboratory results were: ALT 204 U/L; total bilirubin 3.7 mg/dL; albumin 1.9 g/dL; creatinine 0.8 mg/dL; and creatinine clearance 84.0 mL/min. Concomitant medications included hepatitis B immune globulin, lamivudine, tacrolimus, prednisone, insulin, omeprazole, amlodipine, clonidine, Premarin and Provera, calcium carbonate, magnesium and fludrocortisone acetate. On November 2, 1999, the patient was hospitalized for hyperkalemia with a potassium level of 6.7 mEq/L (reference range 3.5-5.0 mEq/L) and acute renal insufficiency with serum creatinine 1.4 mg/dL. The patient was treated for these conditions. The investigator believed that the hyperkalemia might have been due to acute renal failure or direct drug effect from adefovir. The patient was discharged on November 3, 1999 with potassium level of 4.0 mEq/L and serum

creatinine of 0.8 mg/dL. Laboratory testing up to February 2002 did not revealed any further abnormality in serum creatinine levels.