Table 8.2.3A. Serious Adverse Events occurring in 2% of Subcohort A Patients (Post-Liver Transplantation) in Study GS-98-435

	Subcohort A (Post-Liver Transplantation)			
	1A	2A	3A	Total
Number of patients	117	12	67	196
Number of patients with any SAE	18 (15%)	2 (17%)	29 (43%)	49 (25%)
Type of SAE				
Body as a whole	14 (12%)	1 (8%)	13 (19%)	28 (14%)
Fever	2 (2%)	0	4 (6%)	6 (3%)
Ascites	0	0	3 (4%)	3 (2%)
Cellulitis	3 (3%)	0	1 (1%)	4 (2%)
Bacterial infection	1 (1%)	1 (8%)	1 (1%)	3 (2%)
Infection	1 (1%)	0	2 (3%)	3 (2%)
Digestive	7 (6%)	0	11 (16%)	18 (9%)
Hepatic failure	1 (1%)	0	2 (3%)	3 (3%)
Gastrointestinal hemorrhage	0	0	4 (6%)	4 (2%)
Nausea	3 (3%)	0	1 (1%)	4 (2%)
Vomiting	2 (2%)	0	1 (1%)	3 (2%)
Metabolic/Nutritional	7 (6%)	0	5 (7%)	12 (6%)
Dehydration	2 (2%)	0	1 (1%)	3 (2%)
Hyperkalemia	1 (1%)	0	2 (3%)	4 (2%)
Abnormal liver function tests	2 (2%)	0	2 (3%)	3 (2%)
Nervous system	1 (1%)	1 (8%)	4 (6%)	6 (3%)
Encephalopathy	1 (1%)	0	2 (3%)	3 (2%)
Respiratory	6 (5%)	0	6 (9%)	12 (6%)
Pleural effusion	1 (1%)	0	2 (3%)	3 (2%)
Pneumonia	2 (2%)	0	3 (4%)	4 (2%)
Urogenital	3 (3%)	0	3 (4%)	6 (3%)
Kidney failure	2 (2%)	0	1 (1%)	3 (2%)

(Source: NDA Safety Update, Volume 2, Table 9)

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Table 8.2.3B. Serious Adverse Events occurring in 2% of Subcohort B Patients (Waitlisted for Liver Transplantation) in Study GS-98-435

	Subcohort B (Waitlisted for Liver Transplant)			
	1B	2B	3B	Total
Number of patients	46	2	80	128
Number of patients with any SAE	9 (20%)	0	28 (35%)	37 (29%)
Type of SAE				
Body as a whole	3 (7%)	0	10 (13%)	13 (10%)
Sepsis	2 (4%)	0	4 (5%)	6 (5%)
Ascites	0	0	3 (4%)	3 (2%)
Multiorgan failure	0	0	2 (3%)	2 (2%)
Digestive	3 (7%)	0	16 (20%)	19 (15%)
Hepatic failure	1 (2%)	0	8 (10%)	9 (7%)
Gastrointestinal hemorrhage	0	0	2 (3%)	2 (2%)
Esophageal hemorrhage	0	0	2 (3%)	2 (2%)
Hepatorenal syndrome	0	0	2 (3%)	2 (2%)
Diarrhea	1 (2%)	0	1 (1%)	2 (2%)
Nervous system	2 (4%)	0	5 (6%)	7 (5%)
Encephalopathy	1 (2%)	0	4 (5%)	5 (4%)
Respiratory	2 (4%)	0	5 (6%)	7 (5%)
Apnea	2 (4%)	0	2 (3%)	4 (3%)
Pleural effusion	0	0	2 (3%)	2 (2%)
Urogenital	2 (4%)	0	9 (11%)	11 (9%)
Kidney failure	2 (4%)	0	5 (6%)	7 (5%)

(Source: NDA Safety Update, Volume 2, Table 9)

An additional 54 serious adverse events in 26 patients were reported in the Safety Update (data cutoff on February 28, 2002, for study GS-98-435. All but one of these events (a case of elevated liver enzymes) were considered by the investigators as related to study drug.

Of note are the following cases:

- Case # 1 (Patient ID # 450-2257; cohort 1A): A 12-year-old Asian female with lamivudine-resistant HBV and status post combine kidney/liver transplant (March 12, 1999), was granted a protocol exception due to age. The patient started adefovir 10 mg daily on November 16, 1999. Baseline laboratory results were: ALT 376 U/L; total bilirubin 0.3 mg/dL; albumin 3.4 g/dL; and creatinine 0.4 mg/dL. On April 4, 2000, she was hospitalized for exacerbation of hepatitis with ALT 418 U/L and liver biopsy showing marked acute and chronic activity. The HBsAg was positive and HBeAg was negative. She was discharged on April 18, 2000. The investigator attributed the increase in liver enzymes to decrease in HBV DNA levels and "immune flare." Follow-up laboratory tests in June 2000 showed ALT 35 U/L, bilirubin 0.2 mg/dL, albumin 3.8 g/dL, and creatinine 0.5 mg/dL. On July 11, 2000, laboratory testing revealed negative HBsAg.

- Case # 2 (Patient ID # 545-2284; cohort 3A): A 40-year-old Turkish male with history of thrombocytopenia (50,000/mL on average) and status post liver transplantation started adefovir 10 mg every other day on May 10, 2000, due to baseline creatinine of 2.2 mg/dL. Concomitant medications included lamivudine, cyclosporine, and amlodipine. Following a subsequent creatinine measurement of 1.6 mg/dL in June 2000, adefovir dose was changed to 5 mg daily. On August 22, 2000, his platelet count decreased to 19,000/mL (reference range 150,000-350,000/mL). Adefovir treatment was interrupted. The next day, the patient was hospitalized for oral mucosal hemorrhage; the platelet count was 1,000/mL. Platelet transfusion did not result in significant increase in platelet count. On August 25, 2000, the patient began steroid therapy and platelet count increased to 32,000/mL on August 29, 2000. Due to a normal bone marrow examination, the investigator considered a diagnosis of medication-related autoimmune thrombocytopenia. The event was considered resolved in November 2000. It was unclear when adefovir was restarted. However, the patient was permanently discontinued from the study on January 19, 2001.

- Case # 3 (Patient ID # 801-2009; cohort 1A): A 34-year-old white male status post liver transplant on June 17, 1997, started adefovir 10 mg daily on September 22, 1999. Baseline laboratory results were: ALT 109 U/L; total bilirubin 0.3 mg/dL; albumin 3.5 g/dL; creatinine 1.0 mg/dL; and HBV DNA 7.6 $\log_{10}$ copies/mL. Concomitant medications included lamivudine, tacrolimus, and co-trimoxazole. On January 1, 2000, the patient was hospitalized with nausea, vomiting, fever, myalgia, and right upper quadrant discomfort. Laboratory tests revealed ALT 529 U/L and AST 236 U/L. No serum HBV DNA level was obtained. He was discharged three days later. A liver biopsy on January 14, 2000 showed inflammation and fibrosis unchanged from previous biopsy in September 1999 and no evidence of rejection. Subsequent laboratory results revealed gradual decrease of ALT and serum HBV DNA levels (ALT was 31 U/L and HBV DNA 3.9 $\log_{10}$ copies/mL at week 88). The investigator assessed the event as probably related to adefovir treatment.

  Reviewer's Comment

  The increase in transaminases in January 2000 could have been related to an "immune flare" associated with suppression of HBV DNA (please see case 450-2257 above)

8.3. Dropouts and Other Significant Adverse Events

8.3.1. Overall Profile of Dropouts

Please see section 7.1 for profile of dropouts in studies GS-98-437 and GS-98-438. In study GS-98-435, a total of 17 patients (9%) in cohorts 1A, 2A, and 3A, and thirteen patients (10%) in cohorts 1B, 2B, and 3B discontinued study drug. Data on patient disposition in this study are summarized in Table 8.3.1.

Table 8.3.1. Patient Disposition in Study GS-98-435

	Treatment Group					
	1A	2A	3A	1B	2B	3B
Number of patients	117	12	67	46	2	80
Number discontinued	6 (5%)	0	11 (16%)	2 (4%)	0	11 (14%)
Reason for discontinuation						
Adverse event	2 (2%)	0	2 (3%)	0	0	3 (4%)
Patient request	0	0	0	0	0	1 (1%)
Death	4 (3%)	0	0	2 (4%)	0	7 (5%)
Lost to follow-up	0	0	9 (13%)	0	0	1 (1%)
Other reason	0	0	0	0	0	1 (1%)

(Source: NDA Safety Update, Volume 2, Table 8)

8.3.2. Adverse Events Leading to Discontinuation of Study Drug

8.3.2.1.Study GS-98-437

Table 8.3.2A summarizes all adverse events that led to discontinuation of study medication in study GS-98-437 in the first 48 weeks, and Table 8.3.2B for those in the second 48 weeks. A total of ten patients (2%), five in the ADV 30 mg group, four in the ADV 10 mg group, and one in the placebo group, discontinued study drug due to adverse events. Please see section 8.2 above for narratives of notable cases.

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Table 8.3.2A. Adverse Events Leading to Discontinuation of Study Drug in Study GS-98-437 in the First 48 Weeks

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number discontinued due to AE	5(3%)	4 (2%)	1 (< 1%)
Type of AE			
Abnormal liver function tests	0	3 (2%)	0
Creatinine increase	1 (< 1%)	0	0
Fanconi-like syndrome	1 (< 1%)	0	0
Headache	1 (< 1%)	0	0
Abdominal pain	1 (< 1%)	0	0
Myocardial infarction	1 (< 1%)	0	0
Nausea	1 (< 1%)	0	1 (< 1%)
Maculopapular rash	0	1 (< 1%)	0
Pruritus	0	1 (< 1%)	0
Amblyopia	1 (< 1%)	0	0

(Source: NDA 21-449, Volume 112, Table 13)

Table 8.3.2B. Adverse Events Leading to Discontinuation of Study Drug in Study GS-98-437 in the Second 48 Weeks

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo
Number of patients	138	85	70	142
Number discontinued due to AE	0	0	1 (1%)	4 (3%)
Type of AE:				
Scleroderma	0	0	0	1 (< 1%)
Abnormal liver function tests	0	0	1 (1%)	3 (2%)

(Source: NDA 21-449, Volume 113, Table 10)

8.3.2.2.Study GS-98-438

Only one patient (ID # 0454-2518), a 45-year-old Asian male who was randomized to the ADV 10 mg group, discontinued the study at week 32 due to HIV illness.

8.3.2.3.Study GS-98-435

Per NDA Safety Update of June 7, 2002, nine patients (5%) in subcohort A (post-liver transplantation) discontinued study drug due to adverse events

(seven due to serious adverse events). All but one case were considered unrelated to study drug by the investigators. The remaining cases were attributed to the underlying disease processes. Eight patients (6%) in subcohort B (waitlisted for liver transplantation) discontinued the study due to serious adverse events. Similarly, only one case was considered related to study drug by the investigators. Tables 8.3.2.3A and 8.3.2.3B summarize adverse events leading to study drug discontinuation in subcohorts A and B, respectively.

Table 8.3.2.3A. Adverse Events Leading to Discontinuation of Study Drug in Subcohort A (Post-Liver Transplantation) in Study GS-98-435

	Subcohort A (Post-Liver Transplantation)			
	1A	2A	3A	Total
Number of patients	117	12	67	196
Number discontinued study drug	4 (3%)	0	5 (7%)	9 (5%)
Type of AE				
Body as a whole	1 (1%)	0	1 (1%)	2 (1%)
Ascites	0	0	1 (1%)	1 (1%)
Cardiovascular	0	0	2 (3%)	2 (1%)
Hypotension	0	0	1 (1%)	1 (1%)
Myocardial infarction	0	0	1 (1%)	1 (1%)
Digestive	1 (1%)	0	1 (1%)	2 (1%)
Hepatic failure	1 (1%)	0	1 (1%)	2 (1%)
Lymphatic	1 (1%)	0	1 (1%)	2 (1%)
Lymphoma	1 (1%)	0	0	1 (1%)
Thrombocytopenia	0	0	1 (1%)[1]	1 (1%)
Respiratory	1 (1%)	0	1 (1%)	2 (1%)
Apnea	1 (1%)	0	0	1 (1%)
Dyspnea	0	0	1 (1%)	1 (1%)
Urogenital	2 (2%)	0	1 (1%)	3 (2%)
Kidney failure	1 (1%)	0	1 (1%)	2 (1%)

[1] Considered related to study drug by the investigator.
(Source: NDA Safety Update, Volume 2, Table 10)

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Table 8.3.2.3B. Adverse Events Leading to Discontinuation of Study Drug in Subcohort B (Waitlisted for Liver Transplantation) in Study GS-98-435

	Subcohort B (Waitlisted for Liver Transplant)			
	1B	2B	3B	Total
Number of patients	46	2	80	128
Number discontinued study drug	1 (2%)	0	7 (9%)	8 (6%)
Type of AE				
Body as a whole	0	0	2 (3%)	2 (2%)
Sepsis	0	0	2 (3%)	2 (2%)
Digestive	0	0	5 (6%)	5 (4%)
Hepatic failure	0	0	1 (1%)	1 (1%)
Hepatorenal syndrome	0	0	2 (3%)	2 (2%)
Esophageal hemorrhage	0	0	1 (1%)	1 (1%)
Gum bleeding	0	0	1 (1%)	1 (1%)
Metabolic/Nutritional	0	0	1 (1%)	1 (1%)
Abnormal liver function tests	0	0	1 (1%)[1]	1 (1%)
Respiratory	0	0	1 (1%)	1 (1%)
Lung Hemorrhage	0	0	1 (1%)	1 (1%)
Uncoded	1 (2%)	0	0	1 (1%)
Aspergillosis	1 (2%)	0	0	1 (1%)

[1] Considered related to study drug by the investigator.
(Source: NDA Safety Update, Volume 2, Table 10)

8.4. Adverse Event Incidence Tables

8.4.1. Selected Adverse Event Tables

8.4.1.1.Study GS-98-437

Grade 3 or 4 (severe) adverse events in the first 48 weeks of study GS-98-437 are summarized in Table 8.4.1.1A. A total of 46 patients (9%) reported severe adverse events, nine (5%) in the ADV 30 mg group, eight (5%) in the ADV 10 mg group, and five (3%) in the placebo group. The investigators attributed events in only 22 patients as possible/probably related to study drug.

In the second 48 weeks of the study, a total of 24 patients (6%) experienced severe adverse events, eight (6%) in the placebo to ADV 10 mg group, one (1%) in the ADV 10 mg to ADV 10 mg group, six (9%) in the ADV 10 mg to placebo group, and nine (6%) in the ADV 30 mg to placebo group. Only events reported in 14 patients (3%) were considered by the investigators as possibly/probably related to study drug. The adverse event profile was not significantly different from that seen in the first 48 weeks.

Table 8.4.1.1A. Severe Adverse Events in the First 48 Weeks in Study GS-98-437

	Treatment Group			
	ADV 30 mg	ADV 10 mg	Placebo	Total
Number of ITT patients	173	171	167	511
Number with any severe AE	15 (9%)	17 (10%)	14 (8%)	46 (9%)
Type of severe AE:				
Body as a whole	5 (3%)	7 (4%)	5 (3%)	14 (3%)
Abdominal pain	3 (2%)	0	1 (< 1%)	4 (< 1%)
Headache	1 (< 1%)	2 (1%)	1 (< 1%)	4 (< 1%)
Chest pain	0	2 (1%)	0	2 (< 1%)
Flu-like syndrome	1 (< 1%)	0	1 (< 1%)	2 (< 1%)
Asthenia	0	0	1 (< 1%)	1 (< 1%)
Back pain	0	0	1 (< 1%)	1 (< 1%)
Pelvic pain	1 (< 1%)	1 (< 1%)	0	1 (< 1%)
Fever	1 (< 1%)	1 (< 1%)	0	1 (< 1%)
Viral infection	0	0	2 (1%)	1 (< 1%)
Cardiovascular	3 (2%)	1 (< 1%)	1 (< 1%)	5 (<1%)
Coronary artery syndrome	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Myocardial infarct	1 (< 1%)	0	0	1 (< 1%)
Postural hypotension	1 (< 1%)	0	0	1 (< 1%)
Syncope	1 (< 1%)	0	0	1 (< 1%)
Digestive	1 (< 1%)	1 (< 1%)	2 (1%)	4 (< 1%)
Cholecystitis	1 (< 1%)	0	0	1 (< 1%)
Flatulence	0	0	1 (< 1%)	1 (< 1%)
Gastroenteritis	0	1 (< 1%)	0	1 (< 1%)
Nausea	0	0	1 (< 1%)	1 (< 1%)
Metabolic/Nutritional	5 (3%)	8 (5%)	4 (2%)	17 (3%)
Weight loss	0	1 (< 1%)	0	1 (< 1%)
Nervous	1 (< 1%)	0	1 (< 1%)	2 (< 1%)
Dizziness	1 (< 1%)	0	0	1 (< 1%)
Neuropathy	0	0	1 (< 1%)	1 (< 1%)
Respiratory	0	1 (< 1%)	0	1 (< 1%)
Rhinitis	0	1 (< 1%)	0	1 (< 1%)
Pharyngitis	0	2 (1%)	0	2 (< 1%)
Skin	0	2 (1%)	1 (< 1%)	3 (< 1%)
Maculopapular rash		1 (< 1%)	1 (< 1%)	2 (< 1%)
Herpes simplex	0	1 (< 1%)	0	1 (< 1%)
Pruritus	0	1 (< 1%)	0	1 (< 1%)
Urogenital	2 (1%)	1 (< 1%)	0	3 (< 1%)
Epididymitis	1 (< 1%)	0	0	1 (< 1%)
Fanconi syndrome	1 (< 1%)	0	0	1 (< 1%)
Testicular disorder	0	1 (< 1%)	0	1 (< 1%)

(Source: NDA 21-449, Volume 112, Table 37)

8.4.1.2.Study GS-98-438

Grade 3 or 4 (severe) adverse events in the first 48 weeks of study GS-98-438 are presented in Table 8.4.1.2A. A total of 13 patients (7%) experienced

severe adverse events, seven (6%) in the ADV 10 mg group, and six (10%) in the placebo group. Only events reported in two of these patients were assessed by the investigators as possibly/probably related to study drug. There were no severe adverse events reported in the second 48 weeks of this study.

Table 8.4.1.2A. Severe (Grade 3/4) Adverse Events in the First 48 Weeks in Study GS-98-438

	Treatment Group		
	ADV 10 mg	Placebo	Total
Number of ITT patients	123	61	184
Number with severe AE	7 (6%)	6 (10%)	13 (7%)
Type of severe AE:			
Body as a whole	4 (3%)	2 (3%)	6 (3%)
Abdominal pain	1 (< 1%)[1]	0	1 (< 1%)
Abscess	0	1 (2%)	1 (< 1%)
Asthenia	1 (< 1%)[1]	0	1 (< 1%)
Headache	0	1 (2%)	1 (< 1%)
HIV infection	1 (< 1%)	0	1 (< 1%)
Pain	1 (< 1%)	0	1 (< 1%)
Viral infection	1 (< 1%)	0	1 (< 1%)
Cardiovascular	0	1 (2%)	1 (< 1%)
Cerebral ischemia	0	1 (2%)	1 (< 1%)
Digestive	1 (< 1%)	0	1 (< 1%)
Rectal disorder	1 (< 1%)	0	1 (< 1%)
Hematologic	1 (< 1%)	0	1 (< 1%)
Thrombocytopenia	1 (< 1%)	0	1 (< 1%)
Metabolic/Nutritional	0	2 (3%)	2 (1%)
Nervous	0	1 (2%)	1 (< 1%)
Neuritis	0	1 (2%)	1 (< 1%)
Respiratory	1 (< 1%)	0	1 (< 1%)
Pharyngitis	1 (< 1%)	0	1 (< 1%)
Urogenital	1 (< 1%)	0	1 (< 1%)
Urinary tract infection	1 (< 1%)	0	1 (< 1%)

[1] Event assessed by investigator as possibly/probably related to study drug.
(Source: NDA 21-449, Volume 146, Table 34)

8.4.1.3.Study GS-98-435

A total of 84 patients (26%) in this study experienced grade 3 or 4 (serious) adverse events. These are summarized in Table 8.4.1.3. Two patients in cohort 2B (patients who were previously enrolled in a compassionate study GS-99-451i and waitlisted for liver transplantation) did not report any severe adverse events. In general, patients in cohorts 3A and 3B, i.e., those with significant renal, hepatic, hematologic dysfunction, or other underlying disease/condition, reported more adverse events compared to those in cohorts

1A, 2A, and 1B, which consisted of patients with relatively milder disease. Adverse events reported as "renal failure" will be discussed in detail under section 8.5.3.1.3.

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Table 8.4.1.3A. Severe (Grade 3/4) Adverse Events in Study GS-98-435

	Treatment Cohort					
	1A	2A	3A	1B	3B	Total[1]
Number of patients	117	12	67	46	80	324
Number with severe AE	20 (11%)	3 (25%)	27 (40%)	7 (15%)	27 (34%)	84 (26%)
Type of SAE						
Body as a whole	9 (8%)	2 (17%)	13 (19%)	4 (9%)	15 (19%)	43 (13%)
Fever	0	0	2 (3%)	0	0	2 (< 1%)
Epistaxis	0	0	0	0	1 (1%)	1 (< 1%)
Asthenia	2 (2%)	0	0	0	2 (2%)	4 (1%)
Pain	2 (2%)	2 (17%)	1 (1%)	1 (2%)	1 (1%)	7 (2%)
Edema	1 (<1%)	0	1 (1%)	0	0	2 (< 1%)
Jaundice	0	0	2 (3%)	1 (2%)	0	3 (< 1%)
Sepsis	2 (2%)	0	0	1 (2%)	4 (5%)	7 (2%)
Ascites	0	0	1 (1%)	0	4 (5%)	5 (1%)
Halitosis	0	0	1 (1%)	0	1 (1%)	2 (< 1%)
Hypertension	0	0	1 (1%)	0	0	1 (< 1%)
Hypotension	0	0	0	0	2 (2%)	2 (< 1%)
Cachexia	1 (<1%)	0	0	0	0	1 (< 1%)
Cellulitis	1 (<1%)	0	0	0	1 (1%)	2 (< 1%)
Peritonitis	1 (<1%)	0	0	0	0	1 (< 1%)
Appendicitis	0	1 (8%)	0	0	0	1 (< 1%)
Sinusitis	0	0	0	0	1 (1%)	1 (< 1%)
Infection	0	0	3 (4%)	0	0	3 (< 1%)
Fungal infection	0	0	0	1 (2%)	0	1 (< 1%)
Abscess	0	0	2 (3%)	0	0	2 (< 1%)
Multiorgan failure	1 (<1%)	0	0	0	1 (1%)	2 (< 1%)
Overdose	0	0	1 (1%)	0	1 (1%)	2 (< 1%)
Cardiovascular	2 (2%)	0	5 (7%)	0	2 (2%)	9 (3%)
Chest pain	1 (<1%)	0	1 (1%)	0	1 (1%)	3 (< 1%)
Myocardial ischemia	1 (<1%)	0	0	0	0	1 (< 1%)
Myocardial infarct	0	0	1 (1%)	0	0	1 (< 1%)
Pericardial effusion	0	0	1 (1%)	0	0	1 (< 1%)
Cardiac arrest	0	0	1 (1%)	0	0	1 (< 1%)
Carotid occlusion	0	0	1 (1%)	0	0	1 (< 1%)
Hepatic art. stenosis	0	0	0	0	1 (1%)	1 (< 1%)
Digestive	5 (4%)	0	12 (18%)	2 (4%)	17 (21%)	36 (11%)
Hepatitis	0	0	0	1 (2%)	0	1 (< 1%)
Hepatic failure	2 (2%)	0	2 (3%)	0	10 (12%)	14 (4%)
GI hemorrhage	0	0	3 (4%)	1 (2%)	2 (2%)	6 (2%)
Esoph. hemorrhage	1 (<1%)	0	0	0	2 (2%)	3 (< 1%)
Hepatorenal syndm.	0	0	1 (1%)	0	3 (4%)	4 (1%)
Reflux esophagitis	0	0	1 (1%)	0	0	1 (< 1%)
Nausea	2 (2%)	0	1 (1%)	0	0	3 (< 1%)
Vomiting	1 (<1%)	0	1 (1%)	0	0	2 (< 1%)
Diarrhea	0	0	0	0	1 (1%)	1 (< 1%)
Cholangitis	0	0	2 (3%)	0	2 (2%)	4 (1%)

(Source: NDA 21-449 Safety Update, Listing 12)

Table 8.4.1.3A. Severe (Grade 3/4) Adverse Events in Study GS-98-435 (Continued)

	Treatment Cohort					
	1A	2A	3A	1B	3B	Total
Number of patients	117	12	67	46	80	324
Number with severe AE	20 (11%)	3 (25%)	27 (40%)	7 (15%)	27 (34%)	84 (26%)
Type of SAE						
Digestive (continued)	5 (4%)	0	12 (18%)	2 (4%)	17 (21%)	36 (11%)
Abd. distension	0	0	1 (1%)	0		1 (< 1%)
Colon cancer	0	0	0	0	1 (1%)	1 (< 1%)
Bile leakage	0	0	0	0	1 (1%)	1 (< 1%)
Hepatoma	0	0	1 (1%)	0		1 (< 1%)
Metabolic/Nutrition	13 (11%)	0	8 (12%)	1 (2%)	4 (5%)	26 (8%)
Dehydration	1 (<1%)	0	1 (1%)	0	0	2 (< 1%)
Weigh loss	0	0	0	0	1 (1%)	1 (< 1%)
Uremia	0	0	1 (1%)	0	0	1 (< 1%)
Hematologic	5 (4%)	0	3 (4%)	2 (4%)	2 (2%)	12 (4%)
Lymphoma	1 (<1%)	0	0	0	0	1 (< 1%)
Coagulation disorder	0	0	0	1 (2%)	0	1 (< 1%)
Anemia	0	0	1 (1%)	0	1 (1%)	2 (< 1%)
Pancytopenia	0	0	1 (1%)	0	0	1 (< 1%)
Leukopenia	0	0	1 (1%)	0	0	1 (< 1%)
Thrombocytopenia	2 (2%)	0	2 (3%)	0	0	4 (1%)
Thrombosis	2 (2%)	0	0	2 (4%)	1 (1%)	5 (1%)
Musculoskeletal	0	0	0	0	2 (2%)	2 (< 1%)
Arthralgia	0	0	0	0	1 (1%)	1 (< 1%)
Arthritis	0	0	0	0	1 (1%)	1 (< 1%)
Muscle cramps	0	1 (8%)	0	0	1 (1%)	1 (< 1%)

(Source: NDA 21-449 Safety Update, Listing 12)

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Table 8.4.1.3A. Severe (Grade 3/4) Adverse Events in Study GS-98-435 (Continued)

	Treatment Cohort					
	1A	2A	3A	1B	3B	Total[1]
Number of patients	117	12	67	46	80	324
Number with severe AE	20 (11%)	3 (25%)	27 (40%)	7 (15%)	27 (34%)	84 (26%)
Type of SAE						
Nervous	3 (3%)	0	5 (7%)	2 (4%)	3 (4%)	13 (4%)
Intracranial bleed	0	0	1 (1%)	0	0	1 (< 1%)
Acute brain syndm.	1 (<1%)	0	0	1 (2%)	0	2 (< 1%)
Encephalopathy	1 (<1%)	0	2 (3%)	0	1 (1%)	4 (1%)
Neuropathy	0	0	0	0	1 (1%)	1 (< 1%)
Paraplegia	0	0	0	1 (2%)	0	1 (< 1%)
Guillain-Barre	0	1 (8%)	0	0	0	1 (< 1%)
Agitation	1 (<1%)	0	0	0	1 (1%)	1 (< 1%)
Migraine	0	0	1 (1%)	0	0	1 (< 1%)
Tremor	0	0	1 (1%)	0	0	1 (< 1%)
Respiratory	5 (4%)	0	5 (7%)	3 (6%)	5 (6%)	18 (6%)
Apnea	1 (<1%)	0	0	3 (6%)	2 (2%)	6 (2%)
Dyspnea	1 (<1%)	0	2 (3%)	0	0	3 (< 1%)
Pleural effusion	1 (<1%)	0	1 (1%)	0	1 (1%)	3 (< 1%)
Pulmonary edema	0	0	0	0	1 (1%)	1 (< 1%)
Pneumonia	1 (<1%)	0	2 (3%)	0	0	3 (< 1%)
Pulm. hemorrhage	0	0	0	0	1 (1%)	1 (< 1%)
Chronic lung disease	1 (<1%)	0	1 (1%)	0	0	2 (< 1%)
Lung cancer	1 (<1%)	0	0	0	0	1 (< 1%)
Urogenital	4 (3%)	0	3 (4%)	2 (4%)	7 (9%)	16 (5%)
Renal failure	4 (3%)	0	3 (4%)	2 (4%)	6 (7%)	15 (5%)
UTI	0	0	0	0	1 (1%)	1 (< 1%)
Accidental injury	0	1 (8%)	0	0	0	1 (< 1%)
Bone fracture	0	1 (8%)	0	0	0	1 (< 1%)

[1] Total for cohorts 1A, 2A, 3A, 1B, 2B, and 3B.
(Source: NDA 21-449 Safety Update, Listing 12)

8.4.2. Common and Drug-Related Adverse Events

8.4.2.1.Study GS-98-437

Adverse events affecting 3% or more of patients in the first 48 weeks are shown in Table 8.4.2.1A and those in the second 48 weeks in Table 8.4.2.1B. The most common complaints were headache, asthenia, abdominal pain, flu-like symptoms, pain, nausea, dyspepsia, flatulence, and myalgia. A significant proportion of patients (26 to 40%) also had pharyngitis. In general, the incidence of adverse event was highest in the ADV 30 mg group, and comparable between the ADV 10 gm group and placebo group. In the second 48 weeks of the study, more patients reported abdominal pain in the ADV 10 mg groups (13 to 14%) compared with the placebo groups (7 to 9%).

Table 8.4.2.1A. Adverse Events Affecting ≥ 3% of Patient ~~in the First~~ 48 Weeks in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Type of AE:			
Body as a whole			
Headache	45 (26%)	43 (25%)	37 (22%)
Asthenia	45 (26%)	42 (25%)	32 (19%)
Abdominal pain	38 (22%)	31 (18%)	32 (19%)
Flu-like syndrome	32 (18%)	28 (16%)	31 (19%)
Pain	13 (8%)	19 (11%)	21 (13%)
Back pain	17 (10%)	11 (6%)	11 (7%)
Fever	11 (6%)	10 (6%)	13 (8%)
Accidental injury	5 (3%)	8 (5%)	10 (6%)
Infection	6 (3%)	7 (4%)	7 (4%)
Chest pain	6 (3%)	5 (3%)	5 (3%)
Neck pain	3 (2%)	6 (4%)	2 (1%)
Digestive			
Nausea	31 (18%)	17 (10%)	23 (14%)
Diarrhea	25 (14%)	23 (13%)	13 (8%)
Dyspepsia	19 (11%)	15 (9%)	14 (8%)
Flatulence	18 (10%)	13 (8%)	10 (6%)
Anorexia	18 (10%)	6 (4%)	9 (5%)
Vomiting	8 (5%)	8 (5%)	4 (2%)
Gastroenteritis	1 (< 1%)	5 (3%)	5 (3%)
Constipation	3 (2%)	5 (3%)	7 (4%)
Metabolic/Nutritional			
Carnitine decreased	5 (3%)	2 (1%)	0
Musculoskeletal			
Myalgia	13 (8%)	6 (4%)	18 (11%)
Arthalgia	15 (9%)	10 (6%)	11 (7%)
Nervous			
Dizziness	18 (10%)	9 (5%)	13 (8%)
Insomnia	9 (5%)	9 (5%)	10 (6%)
Somnolence	6 (3%)	8 (5%)	8 (5%)
Depression	3 (2%)	7 (4%)	7 (4%)
Anxiety	3 (2%)	3 (2%)	5 (3%)
Respiratory			
Pharyngitis	70 (40%)	44 (26%)	54 (32%)
Rhinitis	13 (8%)	23 (13%)	19 (11%)
Cough increased	19 (11%)	11 (6%)	21 (13%)
Bronchitis	5 (3%)	2 (1%)	5 (3%)

Table 8.4.2.1A. Adverse Events Affecting ≥ 3% of Patient in the First 48 Weeks in Study GS-98-437 (Continued from Previous Page)

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Type of AE:			
Urogenital			
Dysuria	5 (3%)	3 (2%)	10 (6%)
Hematuria	3 (2%)	6 (4%)	2 (1%)

(Source: NDA 21-449, Volume 112, Table 34A)

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Table 8.4.2.1B. Adverse Events Affecting ≥ 3% of Patient in ~~the Second~~ 48 Weeks in Study GS-98-437

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo
Number of ITT patients	138	85	70	142
Type of AE:				
Body as a whole				
Abdominal pain	19 (14%)	11 (13%)	5 (7%)	13 (9%)
Headache	18 (13%)	6 (7%)	6 (9%)	13 (9%)
Asthenia	11 (8%)	7 (8 %)	9 (13%)	16 (11%)
Flu-like syndrome	10 (7%)	8 (9%)	4 (6%)	12 (8%)
Pain	8 (6%)	0	4 (6%)	5 (4%)
Back pain	4 (3%)	4 (5%)	1 (1%)	2 (1%)
Fever	1 (< 1%)	2 (2%)	5 (7%)	4 (3%)
Accidental injury	2 (1%)	3 (4%)	0	3 (2%)
Malaise	0	0	2 (3%)	1 (< 1%)
Cardiovascular				
Hypertension	3 (2%)	0	2 (3%)	3 (2%)
Digestive				
Nausea	6 (4%)	3 (4%)	3 (4%)	3 (2%)
Diarrhea	2 (1%)	5 (6%)	4 (6%)	3 (2%)
Dyspepsia	3 (2%)	3 (4%)	4 (6%)	2 (1%)
Anorexia	2 (1%)	1 (1%)	2 (3%)	1 (< 1%)
Constipation	0	3 (4%)	0	1 (< 1%)
Vomiting	1 (< 1%)	2 (2%)	2 (3%)	1 (< 1%)
Musculoskeletal				
Myalgia	5 (4%)	1 (1%)	3 (4%)	1 (< 1%)
Arthalgia	2 (1%)	1 (1%)	6 (9%)	4 (3%)
Nervous				
Dizziness	2 (1%)	1 (1%)	0	6 (4%)
Insomnia	6 (4%)	2 (2%)	0	8 (6%)
Depression	2 (1%)	2 (2%)	2 (3%)	2 (1%)
Respiratory				
Pharyngitis	17 (12%)	7 (8%)	9 (13%)	17 (12%)
Rhinitis	11 (8%)	3 (4%)	2 (3%)	9 (6%)
Cough increased	4 (3%)	3 (4%)	3 (4%)	4 (3%)
Skin				
Rash	7 (5%)	1 (1%)	0	4 (3%)
Pruritus	4 (3%)	0	1 (1%)	1 (< 1%)

(Source: NDA 21-449, Volume 114, Table 15)

8.4.2.2.Study GS-98-438

Adverse events affecting 3% or more of patients in the first 48 weeks are shown in Table 8.4.2.2A. There were no adverse events that occurred in 3% or more of patients in the second 48 weeks in this study. In general, the

incidence of adverse event in this study is lower than that ~~of study GS~~-98-437. The most common adverse events reported by the patients were headache, flu-like symptoms, asthenia, and pain. Again, pharyngitis affected up to 23% of all patients, more in the placebo group than ADV 10 mg group. Similar to that observed in the second 48 weeks of study GS-98-437, abdominal pain was more common in the ADV 10 mg group (15%) than in the placebo group (5%).

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Table 8.4.2.2A. Adverse Events Affecting ≥ 3% of Patient ~~in the First~~ 48 Weeks in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Type of AE:		
Body as a whole		
Headache	29 (24%)	10 (16%)
Asthenia	16 (13%)	10 (16%)
Flu-like syndrome	13 (11%)	13 (21%)
Abdominal pain	18 (15%)	3 (5%)
Back pain	12 (10%)	4 (7%)
Pain	10 (8%)	6 (10%)
Fever	5 (4%)	3 (5%)
Accidental injury	4 (3%)	2 (3%)
Digestive		
Dyspepsia	6 (5%)	2 (3%)
Diarrhea	5 (4%)	2 (3%)
Flatulence	5 (4%)	2 (3%)
Nausea	5 (4%)	2 (3%)
Anorexia	1 (< 1%)	4 (7%)
Vomiting	4 (3%)	1 (2%)
Metabolic/Nutritional		
Carnitine decreased	4 (3%)	1 (2%)
Musculoskeletal		
Myalgia	4 (3%)	1 (2%)
Arthalgia	1 (< 1%)	2 (3%)
Arthritis	0	2 (3%)
Nervous		
Insomnia	6 (5%)	4 (7%)
Somnolence	1 (< 1%)	3 (5%)
Decreased libido	0	2 (3%)
Respiratory		
Pharyngitis	23 (19%)	14 (23%)
Cough	10 (8%)	4 (7%)
Bronchitis	5 (4%)	3 (5%)
Rhinitis	6 (5%)	1 (2%)
Skin		
Fungal dermatitis	1 (2%)	1 (2%)
Pruritus	2 (3%)	2 (3%)

(Source: NDA 21-449, Volume 146, Table 32A)

8.4.2.3.Study GS-98-435

The profile of adverse events affecting 5% or more of all patients in this study is presented in Table 8.4.2.3 below.

Table 8.4.2.3. Adverse Events Affecting ≥ 5% of Patient in Study GS-98-438

	Treatment Cohort		
	A	B	Total
Number of patients	196	128	324
Number with severe AE	140 (71%)	74 (58%)	214 (66%)
Type of SAE			
Body as a whole			
Asthenia	30 (15%)	13 (10%)	43 (13%)
Abdominal pain	19 (14%)	14 (11%)	33 (10%)
Headache	23 (12%)	3 (4%)	26 (8%)
Fever	13 (7%)	7 (5%)	20 (6%)
Flu-like syndrome	14 (7%)	3 (2%)	17 (5%)
Pain	12 (6%)	4 (5%)	16 (5%)
Back pain	11 (6%)	2 (2%)	13 (4%)
Infection	11 (6%)	2 (2%)	13 (4%)
Sepsis	1 (1%)	8 (6%)	9 (3%)
Cardiovascular			
Hypertension	21 (11%)	6 (5%)	27 (8%)
Digestive			
Diarrhea	19 (10%)	11 (9%)	30 (9%)
Hepatic failure	8 (4%)	17 (13%)	25 (8%)
Nausea	19 (10%)	5 (4%)	24 (7%)
Vomiting	13 (7%)	2 (2%)	15 (5%)
Metabolic/Nutritional			
Edema	14 (7%)	4 (3%)	18 (6%)
Musculoskeletal			
Arthralgia	9 (5%)	3 (2%)	12 (4%)
Myalgia	9 (5%)	2 (2%)	11 (3%)
Nervous			
Insomnia	10 (5%)	3 (2%)	13 (4%)
Encephalopathy	3 (2%)	8 (6%)	11 (3%)
Respiratory			
Pharyngitis	23 (12%)	2 (2%)	25 (8%)
Cough increased	12 (6%)	4 (3%)	16 (5%)
Dyspnea	10 (5%)	2 (2%)	12 (4%)
Rhinitis	9 (5%)	2 (2%)	11 (3%)
Skin			
Pruritus	15 (8%)	6 (5%)	21 (7%)
Rash	9 (5%)	3 (2%)	12 (4%)
Urogenital			
Kidney failure	8 (4%)	7 (5%)	15 (5%)

(Source: NDA 21-449, SN 016)

- 8.5. Laboratory Findings

8.5.1. Standard Analyses and Explorations of Laboratory Data

8.5.1.1.Study GS-98-437

Grade 3 (severe) and grade 4 (life-threatening) laboratory abnormalities in the first 48 weeks of the study are summarized in Table 8.5.1.1A. The most common grade 3/4 laboratory abnormalities were increased transaminases and hematuria. The incidence of significant transaminitis in the first 48 weeks of treatment was lower in the adefovir-treated groups compared with placebo group. In the second 48 weeks, a significant proportion of patients in the ADV-to-placebo experienced increase in serum ALT and AST levels following drug discontinuation (Table 8.5.1.1B). Approximately 13% of patients evenly distributed across all treatment groups experienced hematuria in the first 48 weeks of the study and 5% in the second 48 weeks; the reason for which was not clear.

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Table 8.5.1.1A. Grade 3/4 Laboratory Abnormalities 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
Alanine aminotransferase (ALT)			
Grade 3 (> 5-10 x ULN)	25 (15%)	29 (17%)	42 (25%)
Grade 4 (> 10 x ULN)	14 (8%)	17 (10%)	32 (19%)
Aspartate aminotransferase (AST)			
Grade 3 (> 5.0-10 x ULN)	19 (11%)	14 (8%)	31 (19%)
Grade 4 (> 10 x ULN)	3 (2%)	5 (3%)	13 (8%)
γ-glutamyl transpeptidase (GGT)			
Grade 3 (> 5.0-10 x ULN)	6 (4%)	0	3 (2%)
Grade 4 (> 10 x ULN)	1 (< 1%)	0	0
Alkaline phosphatase (AP)			
Grade 3 (> 5.0-10 x ULN)	1 (<1 %)	0	0
Grade 4 (> 10 x ULN)	0	0	0
Total bilirubin			
Grade 3 (> 3.0 mg/dL)	1 (< 1%)	0	2 (1%)
Grade 4 (> 6.0 mg/dL)	0	0	0
Prothrombin time (PT)			
Grade 3 (> .15-3.0 x ULN)	0	1 (< 1%)	0
Grade 4 (> 3 x ULN)	1 (< 1%)	0	0
Amylase			
Grade 3 (> 2.0-5.0 x ULN)	4 (2%)	7 (4%)	6 (4%)
Grade 4 (> 5.0 x ULN)	0	0	0
Creatine kinase (CK)			
Grade 3 (> 4.0-6.0 x ULN)	5 (3%)	8 (5%)	5 (3%)
Grade 4 (> 6.0 x ULN)	10 (6%)	7 (4%)	5 (3%)
Hypophosphatemia			
Grade 3 (1.0-1.4 mg/dL)	5 (3%)	1 (< 1%)	0
Grade 4 (< 1.0 mg/dL)	1 (< 1%)	0	0
Hyperglycemia			
Grade 3 (251-500 mg/dL)	3 (2%)	0	4 (2%)
Grade 4 (> 500 mg/dL)	0	1 (< 1%)	0
Hypoglycemia			
Grade 3 (30-39 mg/dL)	0	0	0
Grade 4 (< 30 mg/dL)	1 (< 1%)	0	0
Hyperkalemia			
Grade 3 (6.6-7.0 mEq/L)	1 (< 1%)	0	0
Grade 4 (> 7.0 mEq/L)	2 (1%)	0	0
Hypocalcemia (ionized)			
Grade 3 (2.0-2.4 mg/dL)	1 (<1%)	4 (2%)	0
Grade 4 (< 2 mg/dL)	0	0	1 (< 1%)
Hyponatremia			
Grade 3 (116-122 mEq/L)	1 (< 1%)	3 (2%)	0
Grade 4 (< 116 mEq/L)	0	0	1 (< 1%)

Table 8.5.1.1A. Grade 3/4 Laboratory Abnormalities in the First 48 Weeks of Study GS-98-437 (continued)

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Neutropenia			
Grade 3 (500-749/mm^3)	0	0	0
Grade 4 (< 500/mm^3)	2 (1%)	0	0
Glycosuria			
Grade 3 (3+)	2 (1%)	1 (< 1%)	5 (3%)
Grade 4 (4+)	0	0	0
Hematuria			
Grade 3 (gross, > 100 RBCs)	23 (13%)	21 (12%)	21 (13%)
Grade 4 (required treatment)	0	0	0

(Source: NDA 21-449, Volume 112, Tables 40A, 40B, 40C, 40D)

Table 8.5.1.1B. Grade 3/4 Laboratory Abnormalities in the Second 48 Weeks of Study GS-98-437

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo
Number of patients	138	85	70	142
ALT				
Grade 3	20 (15%)	4 (5%)	11 (16%)	23 (16%)
Grade 4	2 (1%)	1 (1%)	14 (20%)	26 (18%)
AST				
Grade 3	7 (5%)	0	8 (12%)	16 (11%)
Grade 4	0	0	4 (6%)	15 (11%)

(Source: NDA 21-449, Volume 113, Tables 21A-D)

Table 8.5.1.1C summarizes marked laboratory changes, defined as a shift from grade 0 at baseline to at least grade 3 or from grade 1 at baseline to grade 4, during the first 48 weeks of the study and those in the second 48 weeks of the study are in Table 8.5.1.1D.

Table 8.5.1.1C. Marked Laboratory Abnormalities[1] 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
ALT increase	3 (2%)	4 (2%)	7 (4%)
AST increase	3 (2%)	2 (1%)	6 (4%)
Hyperamylasemia	2 (1%)	0	2 (1%)
Hyponatremia	1 (< 1%)	3 (2%)	1 (< 1%)
Hyperkalemia	2 (1%)	0	0
Hypocalcemia	0	2 (1%)	1 (< 1%)
Hypoglycemia	1 (< 1%)	0	0
Hyperglycemia	0	1 (< 1%)	0
Hypophosphatemia	5 (3%)	1 (< 1%)	0
CK increase	11 (6%)	13 (8%)	9 (5%)
Prolonged prothrombin time	1 (< 1%)	0	0
Neutropenia	2 (< 1%)	0	0
Glycosuria	0	1 (< 1%)	2 (1%)

[1] Defined as a shift from grade 0 at baseline to at least grade 3 or from grade 1 at baseline to grade 4.
(Source: NDA 21-449, Volume 112, Table 41)

Table 8.5.1.1D. Marked Laboratory Abnormalities in the Second 48 Weeks of Study GS-98-437

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo
Number of patients	138	85	70	142
ALT increase	1 (< 1%)	1 (1%)	20 (69%)	39 (28%)
AST increase	1 (< 1%)	0	12 (17%)	26 (18%)
GGT increase	1 (< 1%)	0	1 (1%)	1 (< 1%)
Hyperamylasemia	0	0	0	1 (< 1%)
Hypernatremia	0	1 (1%)	0	1 (< 1%)
Hyperkalemia	0	0	0	1 (< 1%)
Hyperbilirubinemia	0	0	0	1 (< 1%)
CK increase	2 (1%)	1 (1%)	3 (4%)	5 (4%)
Neutropenia	0	1 (1%)	0	0
Glycosuria	2 (1%)	0	0	1 (< 1%)
Hematuria	3 (2%)	2 (2%)	0	3 (2%)

(Source: NDA 21-449, Volume 113, Table 22)

As shown in Table 8.5.1.1D, a significant proportion of patients who were switched from adefovir to placebo in the second 48 weeks of the study

experienced marked ALT/AST abnormalities (indicative of acute exacerbation of hepatitis or "hepatic flare") compared with those who continued adefovir treatment. Most of these events occurred within 12 weeks of drug discontinuation (please also see section 8.5.3.2 for additional information). Therefore, it is important that patients who discontinue adefovir treatment be closely observed for acute exacerbation of the disease.

8.5.1.2.Study GS-98-438

Grade 3 and grade 4 laboratory abnormalities in the first 48 weeks of the study are summarized in Table 8.5.1.2A, and those in the second 48 weeks of the study in Table 8.5.1.2.B. The laboratory abnormalities in this study appear similar to those observed in study GS-98-437.

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Table 8.5.1.2A. Grade 3/4 Laboratory Abnormalities in the First 48 Weeks of Study GS-98-438

	Treatment group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
ALT		
Grade 3	11 (9%)	13 (21%)
Grade 4	2 (2%)	7 (11%)
AST		
Grade 3	4 (3%)	4 (7%)
Grade 4	0	5 (8%)
Total bilirubin		
Grade 3	3 (5%)	1 (< 1%)
Grade 4	0	0
Prothrombin time		
Grade 3	1 (< 1%)	0
Grade 4	0	0
Amylase		
Grade 3	4 (3%)	0
Grade 4	0	0
CK		
Grade 3	4 (3%)	2 (3%)
Grade 4	2 (2%)	3 (5%)
Hyperglycemia		
Grade 3	2 (2%)	1 (2%)
Grade 4	0	0
Hyperkalemia		
Grade 3	1 (< 1%)	0
Grade 4	0	0
Hyponatremia		
Grade 3	0	0
Grade 4	1 (< 1%)	0
Glycosuria		
Grade 3	3 (2%)	1 (2%)
Grade 4	0	0
Hematuria		
Grade 3	10 (8%)	2 (3%)
Grade 4	0	0

(Source: NDA 21-449, Volume 146, Tables 38A, 38B, 38C, 38D)

Table 8.5.1.2B. Grade 3/4 Laboratory Abnormalities in the Second 48 Weeks of Study GS-98-438

	Treatment Group		
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo
Number of ITT patients	60	79	40
ALT			
Grade 3	2 (3%)	2 (3%)	8 (20%)
Grade 4	0	2 (3%)	11 (28%)
AST			
Grade 3	2 (3%)	1 (1%)	6 (15%)
Grade 4	0	1 (1%)	6 (15%)
Total bilirubin			
Grade 3	0	0	1 (3%)
Grade 4	0	0	0
Amylase			
Grade 3	3 (5%)	3 (4%)	1 (3%)
Grade 4	0	0	0
CK			
Grade 3	0	0	1 (3%)
Grade 4	0	1 (1%)	0
Hyperglycemia			
Grade 3	1 (2%)	2 (3%)	0
Grade 4	0	0	0
Hypoglycemia			
Grade 3	0	0	1 (3%)
Grade 4	0	0	0
Hypernatremia			
Grade 3	1 (2%)	0	0
Grade 4	0	0	0
Thrombocytopenia			
Grade 3	0	0	0
Grade 4	1 (2%)	2 (3%)	0
Glycosuria			
Grade 3	2 (3%)	1 (1%)	1 (5%)
Grade 4	0	0	0
Hematuria			
Grade 3	3 (5%)	3 (4%)	1 (3%)
Grade 4	0	0	0

(Source: NDA 21-449, Volume 147, Tables 25A, 25B, 25C, 25D)

Table 8.5.1.2C summarizes marked laboratory changes, defined as a shift from grade 0 at baseline to at least grade 3 or from grade 1 at baseline to grade 4, during the first 48 weeks of the study and those in the second 48 weeks of the study are in Table 8.5.1.2D.

Table 8.5.1.2C. Marked Laboratory Abnormalities[1] in the ~~First 48 W~~eeks of Study GS-98-438

	Treatment group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Laboratory parameter		
ALT increase	0	4 (7%)
AST increase	0	3 (5%)
Hyperamylasemia	0	1 (2%)
Hyponatremia	1 (< 1%)	0
Hyperbilirubinemia	0	2 (3%)
CK increase	5 (4%)	5 (8%)
Prolonged PT	1 (< 1%)	0
Glycosuria	2 (2%)	0

[1] Defined as a shift from grade 0 at baseline to at least grade 3 or from grade 1 at baseline to grade 4.
(Source: NDA 21-449, Volume 146, Table 39)

Table 8.5.1.2D. Marked Laboratory Abnormalities in the Second 48 Weeks of Study GS-98-438

	Treatment Group		
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo
Number of ITT patients	60	79	40
ALT increase	0	2 (3%)	16 (40%)
AST increase	0	0	10 (25%)
Hypernatremia	1 (2%)	0	0
Hypoglycemia	0	0	1 (3%)
Hyperbilirubinemia	0	0	1 (3%)
CK increase	0	1 (1%)	0
Thrombocytopenia	1 (2%)	2 (3%)	2 (5%)
Glycosuria	2 (3%)	1 (1%)	0

(Source: NDA 21-449, Volume 147, Table 26)

Most of the marked ALT/AST abnormalities (indicative of acute exacerbation of hepatitis or "hepatic flare") occurred within 3 months of drug discontinuation (please see section 8.5.3.2. for additional information). Therefore, patients who discontinue drug treatment should be monitored closely for disease exacerbation.

8.5.1.3.Study GS-98-435

Data on grade 3 and grade 4 laboratory abnormalities are presented in Table 8.5.1.3 (please see Table 8.5.3.1.3B for data on serum creatinine and

phosphorus). In general, the laboratory abnormalities reflected the severity of the underlying disease process and associated medical conditions in the patient population. More patients in subcohort B (waitlisted for liver transplantation), particularly cohort 3B (those with significant underlying disease/condition status), had transaminitis, hyperbilirubinemia, hypoalbuminemia, thrombocytopenia, and prolonged prothrombin time as expected.

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Table 8.5.1.3. Grade 3/4 Laboratory Abnormalities in Study GS-98-435

	Treatment Cohort[1]					
	1A	2A	3A	1B	2B	3B
Number of patients	102	11	56	42	2	59
ALT						
Grade 3	19 (19%)	1 (9%)	8 (14%)	3 (7%)	0 (0%)	9 (15%)
Grade 4	2 (2%)	1 (9%)	2 (4%)	4 (10%)		0
AST						
Grade 3	14 (14%)	2 (18%)	11 (20%)	4 (10%)	1 (50%)	6 (10%)
Grade 4	5 (5%)	0	2 (4%)	5 (12%)	0	4 (7%)
Total bilirubin						
Grade 3	5 (5%)	1 (9%)	4 (7%)	8 (19%)	0	10 (17%)
Grade 4	4 (4%)	0	9 (16%)	4 (10%)	0	13 (22%)
Amylase						
Grade 3	3 (3%)	2 (18%)	7 (13%)	3 (7%)	0	3 (5%)
Grade 4	0	0	1 (2%)	0	0	0
Lipase						
Grade 3	1 (1%)	0	1 (2%)	1 (2%)	0	0
Grade 4	1 (1%)	0	0	1 (2%)	0	2 (3%)
CK						
Grade 3	2 (2%)	0	0	0	0	1 (2%)
Grade 4	2 (2%)	0	0	3 (7%)	0	2 (3%)
Hyperglycemia						
Grade 3	13 (13%)	1 (9%)	8 (14%)	2 (5%)	1 (50%)	6 (10%)
Grade 4	1 (1%)	0	0	0	0	0
Hypoalbuminemia						
Grade 3	2 (2%)	0	5 (9%)	1 (2%)	0	6 (10%)
Grade 4	0	0	0	0	0	0
Hyponatremia						
Grade 3	1 (1%)	0	1 (2%)	0	0	0
Grade 4	0	0	0	0	0	0
Hyperkalemia						
Grade 3	2 (2%)	0	1 (2%)	0	0	0
Grade 4	1 (1%)	0	0	0	0	1 (2%)
Hypocalcemia						
Grade 3	0	0	1 (2%)	0	0	1 (2%)
Grade 4	2 (2%)	0	0	0	0	2 (3%)
Thrombocytopenia						
Grade 3	1 (1%)	0	2 (4%)	5 (11%)	0	9 (15%)
Grade 4	0	0	2 (4%)	1 (2%)	0	0
Neutropenia						
Grade 3	1 (1%)	0	2 (4%)	0	0	1 (2%)
Grade 4	0	0	0	0	0	0
PT increased						
Grade 3	0	0	2 (4%)	1 (2%)	0	7 (12%)
Grade 4	0	0	1 (2%)	0	0	0

[1] Subcohort A: post-liver transplantation; subcohort B: waitlisted for liver transplantation
(Source: NDA 21-449, NDA Safety Update, GSI # 016)

8.5.2. Dropouts due to Laboratory Abnormalities

In study GS-98-437, two patients in the ADV 30 mg group discontinued study drug due to Fanconi-like syndrome and elevated serum creatinine, respectively; both during the first 40 weeks of treatment. In study GS-98-435, three patients discontinued study drug due to increase in serum creatinine and one due to abnormal ALT elevation.

8.5.3. Additional Analyses and Explorations of Laboratory Data

8.5.3.1.Nephrotoxicity

Nephrotoxicity was historically shown to be the treatment-limiting toxicity of adefovir therapy at doses of 60 mg and 120 mg daily in clinical studies (GS-96-408, GS-97-417, [redacted] evaluating adefovir for the treatment of HIV infection. It is characterized by gradual, dose-dependent increases of serum creatinine and decreases in serum phosphorus, with a delayed onset for both occurring at 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-like syndrome). Approximately 34% of patients (by Kaplan-Meier estimates) who received adefovir 60 mg daily had serum creatinine increase of 0.5 mg/dL or greater at week 50 in study GS-97-417, compared with 42% who received adefovir 120 mg daily. Approximately 26% of patients in the ADV 60 mg group and 49% in the ADV 120 mg group had serum phosphorus levels of < 2.0 mg/dL at week 50 of treatment. These data are summarized in Table 8.5.3.1.

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Table 8.5.3.1. Kaplan-Meier Estimates for Serum Creatinine Increase 0.5 mg/dL from Baseline and Hypophosphatemia 2.0 mg/dL in Adefovir HIV Studies

	Study GS-97-417		Study GS-96-408 (ADV 120 mg)
	ADV 120 mg group	ADV 60 mg Group	
Number of ITT patients	104	108	403
Creatinine increase			
Proportion of affected patients	42% (wk 50)	34% (wk 50)	42% (wk 48)
Time to onset			
Median	28	28	32
Q1, Q3	20, 29	27, 32	25, 39
Hypophosphatemia			
Proportion of affected patients	49% (wk 50)	26% (wk 50)	44% (wk 48)
Time to onset			
Median	28	28	31
Q1, Q3	28, 29	28, 28	27, 36

(Source: NDA 21-449, Volume 2, Table 43)

8.5.3.1.1. Study GS-98-437

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 summarized in Table 8.5.3.1.1A and in the second 48 weeks in Table 8.5.3.1.1B.

Table 8.5.3.1.1A. Incidence of Any Increased Serum Creatinine to 0.3 mg/dL from Baseline and Hypophosphatemia < 2.0 mg/dL in the First 48 Weeks in 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

(Source: NDA 21-449, Volume 112, Table 40B)

Table 8.5.3.1.1B. Incidence of Any Increased Serum Creatinine to 0.3 mg/dL from Baseline and Hypophosphatemia < 2.0 mg/dL in the Second 48 Weeks in Study GS-98-437

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo
Number of patients	138	85	70	142
Creatinine increase				
Grade 1	0	1 (1%)	0	2 (1%)
Grade 2	0	1 (1%)	0	0
0.3 to < 0.5 mg/dL	14 (10%)	7 (8%)	4 (6%)	8 (6%)
0.5 mg/dL	1 (< 1%)	1 (1%)	1 (1%)	1 (< 1%)
Hypophosphatemia				
Grade 1	3 (2%)	2 (2%)	0	4 (3%)
Grade 2	2 (1%)	0	2 (3%)	4 (3%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0

(Source: NDA 21-449, Volume 114, Table 21B)

The incidence of "confirmed" increase in serum creatinine and hypophosphatemia (defined as two consecutive laboratory measurements) is presented in Table 8.5.3.1.1C. 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 at the next study visit one month later. The proportion of males and females affected by either confirmed serum creatinine increase (0.3 mg/dL from baseline) or confirmed hypophosphatemia (< 2.0 mg/dL, grade 2 or higher) or both was 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.

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Table 8.5.3.1.1C. 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 in 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.
(Source: NDA 21-449, SN 015)

In the second 48 weeks of the study, four patients (3%) in the placebo-to-ADV 10 mg group experienced a confirmed increase in serum creatinine 0.3 mg/dL from baseline. The abnormality occurred within the first 28 weeks of treatment (range: 8-28 weeks). Additionally, three more patients (3%) in the ADV 10 mg-to-ADV 10 mg group also had a confirmed increase in serum creatinine at weeks 52, 72, and 120. These are summarized in Table 8.5.3.1.1D.

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Table 8.5.3.1.1D. Patients with Confirmed Serum Creatinine ~~0.3 mg~~ from Baseline in Study GS-98-437

Patient ID #	Treatment Group	Week at Confirmed Increase	Resolved at Last Dose?[1]	Action at time of Confirmed Increase
0339-3029	ADV 10 to ADV 10	20	Yes	Continued dosing
0381-1128	ADV 10 to ADV 10	52	No	Continued dosing
0473-6088	ADV 10 to ADV 10	32	Yes	Continued dosing
0501-3016	ADV 10 to ADV 10	72	Yes	Continued dosing
0456-7043	ADV 10 to ADV 10	32	Yes	Reduced to 5 mg
0511-4057	ADV 10 to ADV 10	36	Yes	Continued dosing
0516-7010	ADV 10 to ADV 10	40	Yes	Reduced to 5 mg
0518-2028	ADV 10 to ADV 10	40	Yes	Continued dosing
0529-1110	ADV 10 to ADV 10	120	Yes	Continued dosing
0511-4027	ADV 10 to placebo	20	Yes	Reduced to 5 mg
0329-1072	ADV 10 to placebo	28	No	Continued dosing
0516-7020	ADV 10 to placebo	44	Yes	Reduced to 5 mg
0338-3010	Placebo to ADV 10	12	No	Continued dosing
0339-3013	Placebo to ADV 10	8	Yes	Continued dosing
0532-1054	Placebo to ADV 10	28	No	Continued dosing
1223-6077	Placebo to ADV 10	20	Yes	Continued dosing

[1] Resolved to 0.2 mg/dL from baseline at last visit on drug
(Source: NDA 21-449, Response to FDA Request of July 8, 2002)

Therefore, the overall incidence of confirmed increase in serum creatinine to 0.3 mg from baseline in patients who received adefovir 10 mg daily dose was 4% (13 of 309 patients) after 48 weeks of treatment compared with less than 1% (1 patient) in the placebo group. This incidence, by Kaplan-Meier estimate, was 9% by week 96 of adefovir treatment.

8.5.3.1.2. Study GS-98-438

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 summarized in Table 8.5.3.1.2A and in the second 48 weeks in Table 8.5.3.1.2B.

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Table 8.5.3.1.2A. Incidence of Any Increased Serum Creatinine to 0.3 mg/dL from Baseline and Hypophosphatemia to < 2.0 mg/dL in the First 48 Weeks in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Creatinine increase		
Grade 1 (1.5 to 2.0 mg/dL)	1 (< 1%)	0
Grade 2 (2.1 to 3.0 mg/dL)	0	0
0.3 to < 0.5 mg/dL from baseline	22 (18%)	8 (13%)
0.5 mg/dL from baseline	2 (2%)	1 (3%)
Hypophosphatemia		
Grade 1 (2.0 to 2.4 mg/dL)	6 (5%)	1 (2%)
Grade 2 (1.5 to 1.9 mg/dL)	4 (3%)	1 (2%)
Grade 3 (1.0 to 1.4 mg/dL)	0	0
Grade 4 (< 1.0 mg/dL)	0	0

(Source: NDA 21-449, Volume 146, Table 38B)

Table 8.5.3.1.2B. Incidence of Any Increased Serum Creatinine to 0.3 mg/dL from Baseline and Hypophosphatemia to < 2.0 mg/dL in the Second 48 Weeks in Study GS-98-438

	Treatment Group		
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo
Number of ITT patients	60	79	40
Creatinine increase			
Grade 1	0	1 (1%)	0
Grade 2	0	0	0
0.3 to < 0.5 mg/dL	4 (7%)	8 (10%)	7 (18%)
0.5 mg/dL	1 (2%)	0	0
Hypophosphatemia			
Grade 1	2 (3%)	0	3 (8%)
Grade 2	1 (2%)	0	0
Grade 3	0	0	0
Grade 4	0	0	0

(Source: NDA 21-449, Volume 147, Table 25B)

The incidence of confirmed increase in serum creatinine to 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL in the first 48 weeks is presented in Table 8.5.3.1.2C.

Table 8.5.3.1.2C. Incidence of Confirmed Increased Serum Creatinine to 0.3 mg/dL from Baseline and Hypophosphatemia < 2.0 mg/dL in the First 48 Weeks in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Creatinine increase to 0.3 mg/dL	2 (2%)	3 (5%)
Resolved to 0.2 mg/dL[1]	1 (50%)	1 (33%)
Unresolved[2]	1 (50%)	2 (67%)
Number remaining on full dose	1	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.
(Source: NDA 21-449, Response to FDA Request of July 8, 2002)

In the second 48 weeks of the study, three patients (5%) in the placebo-to-ADV 10 mg group compared with one patient in the ADV 10 mg-to-placebo group had a confirmed increase in serum creatinine to 0.3 mg/dL from baseline (range: 8 to 28 weeks). An additional eight patients in the ADV 10 mg-to-ADV 10 mg group also had a confirmed increased in serum creatinine (range: 52 to 92 weeks). These are shown in Table 8.5.3.1.2D.

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Table 8.5.3.1.2D. Patients with Confirmed Serum Creatinine ~~0.3 mg~~ from Baseline in Study GS-98-438

Patient ID #	Treatment Group	Week at Confirmed Increase	Resolved at Last Dose?[1]	Action at time of Confirmed Increase
0035-3520	ADV 10 to ADV 10	52	Yes	Continued dosing
0370-3502	ADV 10 to ADV 10	60	Yes	Continued dosing
0370-3514	ADV 10 to ADV 10	80	No	Continued dosing
0454-2512	ADV 10 to ADV 10	24	Yes	Reduced to 5 mg
0456-4521	ADV 10 to ADV 10	56	Yes	Continued dosing
0474-5508	ADV 10 to ADV 10	72	Yes	Reduced to 5 mg
0510-4514	ADV 10 to ADV 10	80	No	Discontinued[2]
0625-1520	ADV 10 to ADV 10	92	Yes	Continued dosing
0625-1556	ADV 10 to ADV 10	64	Yes	Reduced to 5 mg
0632-2514	ADV 10 to placebo	28	No	Continued dosing
0624-1527	Placebo to ADV 10	28	Yes	Reduced to 5 mg
0510-4513	Placebo to ADV 10	8	No	Continued dosing
0511-4519	Placebo to ADV 10	28	No	Continued dosing

[1] Resolved to 0.2 mg/dL from baseline at last visit on drug
[2] Discontinued drug at week 76 due to creatinine increased to 2.3 mg/dL at week 76 and 1.6 mg/dL at week 80.
(Source: NDA 21-449, Response to FDA Request of July 8, 2002)

Therefore, the overall incidence of confirmed increase in serum creatinine to 0.3 mg/dL from baseline in patients who received adefovir 10 mg daily dose in this study was 3% (5 in 183 patients) in the first 48 weeks compared with 5% (3 of 61 patients) in the placebo group. This incidence, by Kaplan-Meier estimate, is 10% by week 96 of adefovir treatment. These figures are comparable to those observed in study GS-98-437, i.e., 4% and 9%, respectively.

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 8.5.3.1.2D. By week 48, approximately 42% of patients in the ADV 30 mg group experienced increase in serum creatinine 0.3 mg/dL from baseline. Of those who received adefovir 10 mg daily, 4% had similar elevations in serum creatinine compared with 2% in the placebo group. Approximately half of the patients with serum creatinine increase to 0.3 mg/dL from baseline in the ADV 30 mg group experienced the event by week 32, and those in the ADV 10 mg group by week 28.

Approximately 5% of patients in the ADV 30 mg group had [redacted] hypophosphatemia to < 2.0 mg/dL compared with none in the ADV 10 mg group and 1% in the placebo group. The time to onset of hypophosphatemia (grade 1 or higher) in affected adefovir-treated patients (ADV 30 mg group) was approximately 28 week.

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 Tables 8.5.3.1.2.E ant 8.5.3.1.2F, respectively. Approximately 82% and 78% of patients (Kaplan-Meier analysis) in the ADV 10 mg group and ADV 30 mg group had resolution of serum creatinine abnormality by 16 weeks and 20 weeks, respectively. Virtually all patients with hypophosphatemia had resolution of the abnormality with or without oral supplementation within 16 weeks of onset.

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Table 8.5.3.1.2.D. Time to Confirmed Increase in 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%

(Source: NDA 21-449, SN 015, Volume 1, Pages 29, 304, 337)

Table 8.5.3.1.2.E. Time to Resolution of Increased Serum Creatinine to 0.2 mg/dL from Baseline (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 to 0.2 mg/dL						
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%

[1] Number of patients at risk
(Source: NDA 21-449, SN 015, Volume 1, Pages 329, 362)

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Table 8.5.3.1.2.F. Time to Resolution of 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 = 9)[1]		ADV 10 mg (n = 0)[1]		Placebo (n = 2)[1]	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Phosphorus to > 2.0 mg/dL						
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
(Source: NDA 21-449, SN 015, Volume 1, Pages 329, 362)

8.5.3.1.3. Study GS-98-435

The evaluation of nephrotoxicity in this study is complicated by the patients' underlying advanced disease status and further limited by its uncontrolled design. A number of patients in this study had abnormal serum creatinine at baseline (22% in post-liver transplant subcohort A, and 11% in waitlisted for liver transplantation subcohort B) as shown in Table 8.5.3.1.3A. Of those who experienced significant increase in serum creatinine while receiving adefovir, many were also taking concomitant nephrotoxic drugs. Additionally, it is clinically well-known that renal function is often compromised in patients with end-stage liver disease. Nevertheless, a substantial proportion of patients in this study experienced treatment-emergent nephrotoxicity as shown below.

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Table 8.5.3.1.3A, Baseline Serum Creatinine of Study GS-98-435

Baseline Serum Creatinine	Treatment Cohort			
	1A (n = 117)	2A (n = 12)	3A (n = 67)	Total (n = 196)
Grade 1 (1.5 - 2.0 mg/dL)	17 (15%)	3 (25%)	11 (16%)	31 (16%)
Grade 2 (2.1 - 3.0 mg/dL)	2 (2%)	0	6 (9%)	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)
Normal				
Grade 1	1 (2%)	0	3 (4%)	4 (3%)
Grade 2	0	0	0	0
Grade 3	0	0	1 (1%)	1 (< 1%)
Grade 4	0	0	2 (2%)	2 (2%)
Total	1 (2%)	0	6 (7%)	7 (5%)

(Source: NDA 21-449, NDA Safety Update, Volume 2, Appendix 4, Table 16)

The Kaplan-Meier analysis of time to a confirmed increase in serum creatinine 0.3 mg/dL from baseline in subcohort A patients (post-liver transplantation) is provided in Table 8.5.3.1.3C and that in subcohort B patients (waitlisted for liver transplantation) in Table 8.5.3.1.3D.

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Table 8.5.3.1.3C. Kaplan-Meier Estimate of Time to Confirmed Increase in Serum Creatinine to 0.3 mg/dL from Baseline in Subcohort A (Post-Liver Transplantation) in Study GS-98-435

	Treatment Cohort					
	1A (# at risk = 125)		2A (# at risk = 12)		3A (# at risk = 68)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Baseline	0	0	0	0	0	0
> Baseline - week 4	3	2%	0	0	3	4%
> Week 4 - week 8	5	4%	0	0	7	11%
> Week 8 - week 12	8	7%	0	0	8	12%
> Week 12 - week 16	8	7%	1	8%	10	16%
> Week 16 - week 20	10	8%	1	8%	10	16%
> Week 20 - week 24	11	9%	1	8%	10	16%
> Week 24 - week 28	12	10%	1	8%	13	22%
> Week 28 - week 32	14	12%	1	8%	17	31%
> Week 32 - week 36	17	15%	1	8%	17	31%
> Week 36 - week 40	21	19%	2	17%	18	34%
> Week 40 - week 44	22	20%	2	17%	18	34%
> Week 44 - week 48	23	21%	3	28%	19	37%
> Week 48 - week 52	27	26%	4	38%	19	37%
> Week 52 - week 56	27	26%	4	38%	19	37%
> Week 56 - week 60	28	27%	4	38%	19	37%
> Week 60 - week 64	28	27%	4	38%	19	37%
> Week 64 - week 68	28	27%	4	38%	20	41%
> Week 68 - week 72	29	29%	4	38%	21	45%
> Week 72 - week 76	29	29%	4	38%	21	45%
> Week 76 - week 80	30	31%	4	38%	21	45%
> Week 80 - week 84	30	31%	4	38%	21	45%
> Week 84 - week 88	30	31%	4	38%	21	45%
> Week 88 - week 92	30	31%	4	38%	21	45%
> Week 92 - week 96	31	33%	4	38%	21	45%

(Source: NDA 21-449, FDA analysis)

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Table 8.5.3.1.3D. Kaplan-Meier Estimate of Time to Confirmed Increase in Serum Creatinine to 0.3 mg/dL from Baseline in Subcohort B (Waitlisted for Liver Transplantation) in Study GS-98-435

	Treatment Cohort					
	1B (# at risk = 50		2B (# at risk = 2)		3B (# at risk = 87)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Baseline	0	0	0	0	0	0
> Baseline - week 4	0	0	1	50%	3	3%
> Week 4 - week 8	1	2%	1	50%	4	5%
> Week 8 - week 12	5	11%	1	50%	7	9%
> Week 12 - week 16	6	13%	1	50%	9	13%
> Week 16 - week 20	7	16%	1	50%	10	15%
> Week 20 - week 24	8	20%	1	50%	11	17%
> Week 24 - week 28	8	20%	1	50%	11	17%
> Week 28 - week 32	8	20%	1	50%	13	24%
> Week 32 - week 36	9	26%	1	50%	13	24%
> Week 36 - week 40	9	26%	1	50%	14	28%
> Week 40 - week 44	9	26%	1	50%	15	33%
> Week 44 - week 48	9	26%	1	50%	15	33%

[1] Insufficient data after week 48
(Source: NDA 21-449, FDA analysis)

The incidences of confirmed increase in serum creatinine to 0.3 mg/dL from baseline and hypophosphatemia to < 2.0 mg/dL is summarized in Table 8.5.3.1.3E.

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Table 8.5.3.1.3F. Kaplan-Meier Estimate of Time to Confirmed Increase in Serum Creatinine to 0.3 mg/dL from Baseline Hypophosphatemia < 2.0 mg/dL by Week 48 and Week 96 in Study GS-98-435

	Treatment Cohort			
	1A	2A	3A	Total
Number of patients at risk	125	12	68	205
Creatinine increased to 0.3 mg/dL from baseline:				
- by week 48	23 (21%)	3 (28%)	19 (37%)	45 (26%)
- by week 96	31 (34%)	4 (38%)	21 (45%)	56 (37%)
Hypophosphatemia < 2.0 mg/dL				
- by week 48	6 (5%)	1 (8%)	1 (2%)	8 (4%)
- by week 96	8 (9%)	1 (8%)	1 (2%)	10 (6%)
	1B	2B	3B	
Number of patients at risk	50	2	87	139
Creatinine increased to 0.3 mg/dL from baseline:				
- by week 48[1]	9 (26%)	1 (50%)	15 (33%)	25 (30%)
Hypophosphatemia < 2.0 mg/dL				
-by week 48[1]	2 (8%)	0	3 (4%)	5 (5%)

[1] Insufficient data after week 48
(Source: NDA 21-449, FDA analysis)

By week 48, approximately 26% of patients in subcohort A (post-liver transplantation) and 30% of patients in subcohort B (waitlisted for liver transplantation) by Kaplan-Meier analysis had increase in serum creatinine to 0.3 mg/dL from baseline. The proportion of patients with hypophosphatemia < 2.0 mg/dL was similar in each cohort, i.e., 4% in subcohort A and 5% in subcohort B. These figures approached those seen in the adefovir 30 mg daily group in study GS-98-437, i.e., 42% with increase in serum creatinine to 0.3 mg/dL from baseline and 5% with hypophosphatemia to < 2.0 mg/dL.

The applicant performed a similar analysis of nephrotoxicity but using higher cutoff values for creatinine (0.5 mg/dL from baseline) and hypophosphatemia (<1.5 mg/dL, grade 3 toxicity) as shown in Table 8.5.3.1.3F. It should be noted that the analysis was based on smaller number of "at risk" patients.

Table 8.5.3.1.3F. Kaplan-Meier Estimate of Time to Confirmed Increase in Serum Creatinine to 0.5 mg/dL from Baseline and Hypophosphatemia < 1.5 mg/dL by Week 48 and Week 96 in Study GS-98-435

	Treatment Cohort		
	1A	2A	3A
Number of patients at risk	97	9	52
Creatinine increased to 0.5 mg/dL from baseline:			
- by week 48	10 (12%)	0	6 (15%)
- by week 96	18 (33%)	1 (13%)	7 (22%)
Hypophosphatemia < 1.5 mg/dL			
- by week 48	0	1 (8%)	0
- by week 96	0	1 (8%)	1 (3%)
	1B	2B	3B
Number of patients at risk	42	2	64
Creatinine increased to 0.5 mg/dL from baseline:			
- by week 48[1]	5 (26%)	0	10 (30%)
Hypophosphatemia < 1.5 mg/dL			
-by week 48[1]	1 (3%)	0	1 (2%)

[1] Insufficient data after week 48
(Source: NDA 21-449, Safety Update, Volume 2, Table F3)

As an alternate to the use of confirmed increase in serum creatinine ≥ 0.3 mg/dL or 0.5 mg/dL from baseline to evaluate increase in serum creatinine, the applicant also performed an analysis on confirmed increase from baseline in serum creatinine by ≥ 50%. This approach is clinically relevant since serum creatinine is inversely proportional to creatinine clearance. As a rule of thumb, doubling of the serum creatinine level corresponds to a 50% decrease in creatinine clearance from the previous level in the steady state. Therefore, a 50% increase in serum creatinine would reflect a 25% decrease in creatinine clearance, a clinically relevant change. Results of this analysis are summarized in Table 8.5.3.1.3G.

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Table 8.5.3.1.3G. Kaplan-Meier Estimate of Time to Confirmed Increase from Baseline in Serum Creatinine to 50% by Week 48 and Week 96 in Study GS-98-435

	Treatment Cohort		
	1A	2A	3A
Number of patients at risk	97	9	52
Creatinine increased from baseline to ≥ 50%:			
- by week 48	7 (8%)	1 (11%)	6 (17%)
- by week 96	12 (20%)	1 (11%)	6 (17%)
	1B	2B	3B
Number of patients at risk	42	2	64
Creatinine increased from baseline to 50%:			
- by week 48[1]	8 (44%)	0	11 (37%)

[1] Insufficient data after week 48
(Source: NDA 21-449, Safety Update, Volume 2, Table F6)

Of the 26 patients in subcohort A (post-liver transplantation) and 15 in cohort B (waitlisted for liver transplantation) with an increase in serum creatinine ≥ 0.5 mg from baseline (see Table 8.5.3.1.3F), 21 (81%) and four (27%), respectively, had baseline creatinine clearance less than 80 mL/min (indicative of some degree of baseline renal impairment). Therefore, results of the above analyses appeared to indicate that a significant number of patients in subcohort B experienced unexpectedly high incidence of severe nephrotoxicity. A case-by-case review (limited to patients with serum creatinine ≥ 0.5 mg from baseline), however, showed that of the 15 patients who had an increase in serum creatinine to 0.5 mg/dL from baseline, 11 (73%) underwent a liver transplantation (two with post-operative acute renal failure) and also started immunosuppressive drugs. These events appeared to be temporally related to subsequent serum creatinine increases. The case-by-case review also revealed a number of cases, particularly in subcohort A, in which the contributory role of adefovir to treatment-emergent nephrotoxicity could not be ruled out. These cases will be presented under "Case Review" at the end of this section.

These results appear to confirm that a significant number of patients in subcohort A experienced a treatment-emergent shift in (unconfirmed) serum creatinine levels: from normal at baseline to grade 1 or higher (35%); or from grade 1 at baseline to grade 2 or higher (35%), etc.

Resolution of Serum Creatinine Increase:

Of the 26 patients in subcohort A and 15 patients in subcohort B with confirmed increase in serum creatinine to 0.5 mg/dL from baseline, data on resolution of serum creatinine to 0.3 mg/dL (from baseline) were available on 24 patients in subcohort A and 14 patients in subcohort B. These are presented in Table 8.5.3.1.3J.

Table 8.5.3.1.3J. Resolution of Increased Serum Creatinine from 0.5 mg/dL above Baseline to 0.3 mg/dL from Baseline

	Treatment Cohort			
	1A (n = 97)	2A (n = 9)	3A (n = 52)	Total (n = 158)
Number with abnormality	18	1	7	26
Resolved to 0.3 mg/dL	4 (22%)	0	0	4 (15%)
Not resolved	14 (78%)	1 (100%)	7 (100%)	22 (85%)
	1B (n = 42)	2B (n = 2)	3B (n = 64)	Total (n = 108)
Number with abnormality	5	0	10	15
Resolved to 0.3 mg/dL	1 (20%)	0	2 (20%)	3 (20%)
Not resolved	4 (80%)	0	8 (80%)	12 (80%)

(Source: NDA 21-449, Safety Update, Volume 2, Table 19)

Reviewer's Comment

Additional analyses on nephrotoxicity in study GS-98-435 using updated data were subsequently performed in preparation for the Antiviral Drug Advisory Committee meeting on August 6, 2002. Results of these analyses are summarized in Tables 8.5.3.1.3K and 8.5.3.1.3K.

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Table 8.5.3.1.3J. Summary of Treatment-Emergent Nephrotoxicity (Study GS-98-435)

Kaplan-Meier Estimate	*Treatment Cohort*	
	A	*B*[†]
Number of patients at risk	*205*	*139*
Creatinine increase 0.3 mg/dL		
By week 48	*45 (26%)*	*25 (30%)*
By week 96	*56 (37%)*	-
Creatinine increase 0.5 mg/dL		
By week 48	*16 (9%)*	*15 (19%)*
By week 96	*28 (23%)*	-
Hypophosphatemia < 2.0 mg/dL		
By week 48	*8 (4%)*	*5 (5%)*
By week 96	*10 (6%)*	-

[†] *Insufficient data after week 48*

Table 8.5.3.1.3K. Summary of Resolution of Creatinine Abnormality

	Treatment Cohort	
	A	*B*
Number of patients with creatinine 0.5 mg/dL	*28*	*15*
Resolved to 0.3 mg/dL	*4 (14%)*	*3 (20%)*
Not resolved at last visit	*24 (86%)*	*12 (80%)*

Of the 28 patients with increase in serum creatinine to 0.5 mg/dL from baseline in subcohort A (post-liver transplantation patients), the contributory role of adefovir to nephrotoxicity cannot be completely ruled out in 22 cases in a case-by-case review. On the other hand, the renal abnormalities in most cohort B (pre-transplantation) patients (12 out of 15) were most likely secondary to medical complications of liver transplant and the subsequent use of immunosuppressive drugs. Examples of some typical cases where nephrotoxicity is of interest are provided below.

Case Review:

The following cases serve to illustrate the difficulty in interpreting the potential contributory role of adefovir to renal events experienced by the 43 patients mentioned in Table 8.5.3.1.3K. In some cases, the contributory role was reasonably obvious, whereas in some other the contributory role was not completely clear.

- Case # 1 (Patient ID # 477-2290; cohort 3A): 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 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 an increase in serum creatinine to 2.0 mg/dL and a decrease in serum phosphorus to 1.5 mg/dL. Oral phosphate supplementation was initiated. On November 25, 2000, the patient was hospitalized with renal failure (peak serum creatinine 3.5 mg/dL). Adefovir treatment was interrupted. The investigator attributed the renal failure to cyclosporine or adefovir. It is unclear whether adefovir treatment was restarted. However, based on subsequent laboratory test results, it appears that the patient suffered another episode of acute renal failure in September 2001.

  Reviewer's Comment

  Although concurrent use of known nephrotoxic medications was a confounding factor in this case, there exists a concern that adefovir treatment, even at doses of 5 to 10 mg daily, may expose patients with pre-existing renal function impairment to significant risk of acute renal failure.

- Case #2 (Patient ID # 801-2016; cohort 3A): This 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 elevated serum creatinine levels that peaked at 5.7 mg/dL (grade 3). Adefovir treatment was interrupted. The next day, his 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. The 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."

Reviewer's Comment

Although the patient started adefovir at half the usual dose due to pre-existing renal insufficiency, he began to exhibit a gradual increase in serum creatinine to 0.5 mg/dL from baseline (a shift from grade 1 at baseline to grade 2) within the first year of adefovir therapy. By April 2001 (treatment week 72) his serum creatinine was 2.9 mg/dL. In the following month he suffered an episode of acute renal failure as described above. The event appeared to resolve by June 2001, only to recur in January to February 2001 (serum creatinine peaked at 4.3 mg/dL; data not shown). This case is of particular concern since a lower dose of adefovir (5 mg daily), in a patient with significant pre-existing renal impairment, may potentially lead to worsening and irreversible renal damage.

- Case # 3 (Patient ID # 956-2281; cohort 3A): 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, the patient's 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.

Reviewer's Comment

There are no pharmacokinetic data on adefovir 5 mg daily in patients with severe renal function impairment. Nevertheless, this patient experienced rapid onset of renal function impairment following commencement of adefovir treatment. The case illustrates the need for appropriate adefovir dose modification and close monitoring in renally fragile patients.

- Case # 4 (Patient ID # 956-2301; cohort 1A): 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	01/01	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, his 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 treatment 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, the 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 dose was increased to 5 mg daily on January

14, 2001. On January 18, 2001, serum creatinine decreased to 5.8 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, the patient's serum creatinine again increased to 7.7 with a creatinine clearance of 10.8 mL/min. There was no further record on this event.

Reviewer's Comment

This case again illustrates the concern that has been raised elsewhere in this review about the possible association between adefovir 10 mg daily dose and acute renal failure in patients with pre-existing renal function impairment.

- Case # 5 (Patient ID # 643-2022; cohort 3A): 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), the patient's serum creatinine increased to 1.6 mg/dL. By week 24 (May 2000), his serum creatinine was 2.0 mg/dL and adefovir treatment 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.

Reviewer's Comment

By creatinine clearance estimates, this patient's renal function was irreversibly reduced to less than half of the baseline level by week 24 of adefovir treatment. While tacrolimus has been known to be nephrotoxic, the concomitant decrease in phosphorus levels strongly implicates the role of adefovir in this case of renal failure. Interestingly, the investigator did not consider such clinically significant renal deterioration a reportable adverse event.

- Case # 6 (Patient ID # 643-2035; cohort 1A): 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 were 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.

Reviewer's Comment

While both adefovir and concomitant cyclosporine could have contributed to this patient's worsening renal function, the concomitant decrease in phosphorus strongly suggests that adefovir played a greater causal role in this case. The increase in serum creatinine did not appear to be reversible even at a reduced dose of adefovir (5 mg daily). Of note is the fact that the investigator did not consider such clinically significant renal deterioration a reportable adverse event.

- Case # 7 (Patient ID # 593-2104; cohort 3B): 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 are summarized below.

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

Reviewer's Comment

Based on the suggested dose interval adjustment of adefovir for patients on dialysis, this patient should have received adefovir every 7 days following dialysis, not after every dialysis.

- Case # 8 (Patient ID # 454-2307; cohort 3B): 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 a 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 treatment was interrupted 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.

  Reviewer's Comment

  Although the progressive liver failure and concomitant nephrotoxic medications were notable confounding factors, it is likely that adefovir could have contributed to this patient's rapidly worsening renal function.

- Case # 9 (Patient ID # 940-2304; cohort 1B): A 60-year-old man with history of liver decompensation (coagulopathy, esophageal varices, cirrhosis, and ascites), started adefovir 10 mg daily in September 2000. Baseline laboratory results were: ALT 28 U/L; total bilirubin 1.6 mg/dL; albumin 3.2 g/dL; creatinine 1.4 mg/dL; and creatinine clearance 61.9 mL/min. Concomitant medications included lamivudine, diuretics, vitamin K, and propanolol. Relevant laboratory test results were as follows:

Date:	01/00	04/01	07/01	08/01	10/01	12/01	02/02
Creatinine:	1.4	1.7	1.8	2.1	2.3	2.2	2.0
Cr. Cl.:	61.9	49.0	46.3	39.9	37.6	41.4	43.4

  In August 2001, the adefovir dose was reduced to 5 mg daily due to a gradual increase in serum creatinine levels that peaked at 2.3 mg/dL in October 2001. At that time, the patient underwent a liver transplantation and subsequently was started on tacrolimus and HBIg. By the last follow-up, the serum creatinine remained at 2.0 mg/dL.

  Reviewer's Comment

  It is likely that adefovir could have contributed to the progressively worsening renal function in this patient who had had a mild renal impairment at baseline.

- Case # 9 (Patient ID # 622-2006; cohort 3A): 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 a potassium level of 4.0 mEq/L and serum creatinine of 0.8 mg/dL. Laboratory testing up to February 2002 did not revealed further abnormality in serum creatinine levels.

  Reviewer's Comment

  It is likely that adefovir could have contributed to this patient's acute renal insufficiency in November 1999.

Some of the cases listed above and a number of other similar cases point to the fact that adefovir 10 mg daily dose (or even 5 mg daily dose) was not the optimal dose in patients with renal dysfunction. The need for appropriate adefovir dosing in these patients to avoid drug-induced nephrotoxicity cannot be overemphasized.

8.5.3.2.Hepatitis "Flare"

Severe hepatitis "flare" was defined as confirmed transaminase values of > 10 x ULN, and at least one of the following laboratory abnormalities: total bilirubin 2.5 mg/dL and 1.0 mg/dL above baseline; albumin < 3.0 g/L; or prothrombin time 1.5 seconds prolonged.

In the first 48 weeks of study GS-98-437, ALT increase to > 10 x ULN occurred in 14 patients (8%) in the ADV 30 mg group, 17 patients (10%) in the ADV 10 mg group, and 32 patients (19%) in the placebo group. No patient in the ADV 30 mg group or ADV 10 mg group experienced severe hepatic flare compared with two patients in the placebo group, one with hypoalbuminemia and the other with hyperbilirubinemia. In the first 48 weeks of study GS-98-438, two patients (3%) in the ADV 10 mg group and seven patients (6%) in the placebo group had ALT increase to > 10 x ULN. No patient in the ADV 10 mg group had severe hepatic flare compared with

five patients (8%) in the placebo group, three with hyperbilirubinemia, two with hypoalbuminemia, and one with prolonged prothrombin time.

Based on integrated data of both studies GS-98-437 and GS-98-438 for the second 48 weeks, a total of ten patients (6%) in the ADV 10 mg to ADV 10 mg group, 28 (25%) in the ADV 10 mg to placebo group, and five (3%) in the placebo to ADV 10 mg group experienced ALT increase to > 10 x ULN. Of these, one patient (< 1%) in the first group, three (3%) in the second group, and none in the third group, respectively, had severe hepatic flare. All four patients had associated hyperbilirubinemia. One patient (ID # 0381-1022) in the ADV 10 mg to placebo group had transient grade 4 hyperbilirubinemia (peak value of 14 mg/dL) between weeks 60 and 64 and resolved to normal range in subsequent follow-up visits.

Of note were the following cases of severe hepatic flare:

- The first case involved sketchy information reported via MedWatch on a patient with advanced HIV and chronic hepatitis B who was enrolled in study GS-97-423 (Adefovir Dipivoxil Expanded Access program). The patient reportedly experienced a "hepatitis flare" after discontinuation of adefovir and died. Additional information on this case is not available at the time this review is completed.

- The second case involved a 50-year-old white male (ID # 626-1543) in study GS-98-438, who developed severe hepatic flare with jaundice and total bilirubin of 5.6 mg/dL six weeks after completing 96 weeks of therapy with adefovir 10 mg daily. The patient received lamivudine therapy with subsequent resolution of the event six weeks later. The investigator, in this case, assessed the case as secondary to reactivation of chronic hepatitis B and unrelated to study drug.

- In the third case, a 33-year-old Asian male (ID # 456-7044, study GS-98-437) was randomized to receive adefovir 30 mg daily in the first 48 weeks of the study and placebo in the second 48 weeks. Due to medication allocation error, he received adefovir 10 mg daily alternating with placebo during the second 48 weeks. Four weeks after study drug was discontinued (14 weeks after last dose of adefovir), the patient developed severe hepatic flare with jaundice (ALT 1,245 U/L, total bilirubin 9.7 mg/dL). Open-label treatment with adefovir 10 mg daily was restarted and the patient's event resolved in one month. The investigator assessed the event as related to withdrawal of study drug.

- The fourth case involved a 41-year-old man with lamivudine-resistant chronic hepatitis B and history of liver transplantation in 1997. He started adefovir 10 mg daily in September 2001 with elevated ALT (3 x ULN) and AST (4 x ULN) at baseline. He was subsequently hospitalized on

November 9, 2001, due to jaundice and elevated ALT/AST levels. Adefovir treatment was discontinued. The patient continued to have worsening of liver function and subsequently developed multi-organ failure. He expired on November 27, 2001.

Reviewer's Comment

Most cases of severe hepatic flare were associated with cessation of adefovir therapy and may occur up to 12 weeks post-treatment. Two patients have reportedly died of hepatic flare (the first two cases described above). Therefore, it is recommended that the labeling contain a statement on careful monitoring of patients after discontinuation of adefovir therapy and that the duration of off-drug follow-up should be at least 3 to 6 months.

8.5.3.3.Carnitine Changes

In the HIV clinical drug development program, it was observed that high doses of adefovir (125 or 250 mg daily) were associated with decreases in serum carnitine levels. After discontinuation of the drug, serum carnitine levels returned towards baseline. The decrease is thought to be secondary to the fact that the pivaloyloxymethyl group of adefovir binds to carnitine and both are subsequently excreted in the urine. Serum carnitine decrease has been linked with skeletal or cardiac myopathy. Although none of the patients in the HIV program exhibited myopathic changes, it was decided early on that patients in studies GS-98-437 and GS-98-438 be monitored for serum creatinine deficicency.

In study GS-98-437, the median change in serum free carnitine (reference range: 2.3-7.0 μmol/dL) from baseline to week 48 was –2.1 μmol/dL in the ADV 30 mg group, -1.0 μmol/dL in the ADV 10 mg group, compared with 0.6 μmol/dL in the placebo group.

In study GS-98-438, six patients (5%) in the ADV 10 mg group and one (2%) in the placebo group received L-carnitine supplement (250 mg daily) at some time during the study. Of the six patients in the ADV 10 mg group, two had serum carnitine levels below the upper limit of normal at baseline and generally stayed below normal throughout the study.

Reviewer's Comment

It appears that administration of adefovir at the dose of 10 mg daily does not significantly affect serum carnitine levels. Therefore, routine supplementation with L-carnitine is not necessary.

8.6. Withdrawal Phenomena/Abuse Potential

No withdrawal phenomenon with adefovir has been reported. This drug does not have abuse potential.

8.7. Human Reproductive Data

In study GS-98-437, a total of 11 pregnancies in 11 patients (8%) were reported, two in the ADV 30 mg group, six in the ADV 10 mg group and three in the placebo group. Four of these pregnancies occurred in the first 48 weeks of the study, and four in the second 48 weeks. Nine patients elected to have therapeutic abortions. Two patients, one in the ADV 10 mg group and one in the placebo group had live births with no reported congenital abnormalities. In study GS-98-437, one patient in the ADV 10 mg group of study S-98-438 became pregnant during the study (study day 54). She elected to have therapeutic abortion. One patient in study GS-98-435 also became pregnant during the study with estimated delivery date in July 2002.

Reviewer's Comment

Adefovir is a pregnancy category C drug (i.e., a drug for which animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks). It is recommended that the labeling include the appropriate FDA Pregnancy Labeling Task Force category C statement. It is recommended also that a pregnancy registry be established to monitor pregnancy outcome in women who are exposed to adefovir.

8.8. Overdose Experience

Clinical experience of acute overdose of adefovir is limited. To date, there have been no cases of adefovir overdose in clinical studies in patients with chronic hepatitis B.

In the HIV clinical development, there were 11 overdoses reported as serious adverse events. In two of these cases, adefovir were taken at a higher dose than recommended. The first case involved a 39-year-old male who mistakenly took double the intended daily dose of adefovir (120 mg twice daily) for approximately two weeks. The patient also received several concomitant antiretroviral drugs (lamivudine, indinavir) and other medications. During that time, he complained of flatulence, abdominal discomfort, and had a grade 3 ALT elevation. These events resolved with the corrected dose of adefovir. In the second case, a patient with history of depression attempted suicide by ingesting adefovir in unspecified quantities along with other drugs. He was treated with charcoal and supportive therapy and recovered without reported clinical sequelae. In early clinical phases of adefovir in HIV-infected patients, daily doses of adefovir 500 mg for two weeks and 250 mg for 12 weeks have been associated with gastrointestinal effects.

8.9. Summary of Key Adverse Findings

Most clinical adverse events and laboratory abnormalities associated with adefovir treatment were comparable to those seen in the placebo group. However, two key adverse events that are of significant concern are as follows:

- Discontinuation of drug treatment resulted in acute exacerbation of hepatitis in a significant proportion of patients. Up to 69% of patients in study GS-98-438 who switched from the ADV 10 mg group to placebo group experienced a marked ALT shift from normal at baseline to at least grade 3 (5 to 10 X ULN) or grade 1 (1.25 to 2.5 X ULN) at baseline to grade 4 (> 10 X ULN); most within 12 weeks of drug discontinuation. At least two fatal cases have been reported to date.

- Treatment-emergent nephrotoxicity manifesting as an increase in serum creatinine 0.3 mg/dL from baseline occurred in approximately 4% of patients with adequate renal function (mean baseline level of 0.6 and 0.9 mg/dL for women and men, respectively) who received adefovir 10 mg daily dose by week 48 (studies GS-98-437 and GS-98-438). The risk was cumulative with longer treatment duration (up to 10% by Kaplan-Meier analysis) by week 96. However, in patients with various degree of renal dysfunction in study GS-98-435, adefovir 10 mg daily dose probably resulted in significantly higher drug exposure than intended. As a result, nephrotoxicity occurred at appreciably higher frequency in these patients. Up to 26% of post-transplanted patients with renal dysfunction due to chronic immunosuppressive therapy had increase in serum creatinine 0.3 mg/dL (mean baseline level of 1.1 and 1.3 mg/dL for women and men, respectively) by week 48; 37% by week 96. The contributory role of adefovir to worsening renal function in most of these patients could not be completely ruled out due to multiple confounding factors and absence of a control group. The serum creatinine abnormality resolved (decrease to 0.2 mg/dL from baseline) in up to 77% of patients who had adequate renal insufficiency with or without treatment discontinuation or dose reduction. However, up to 86% of patients with renal dysfunction who had increased serum creatinine 0.5 mg/dL did not achieve resolution of serum creatinine (i.e., decrease to 0.3 mg/dL).

9. Pediatric Drug Development Plan

In a clinical development meeting on April 25, 2000, FDA requested that the applicant submit a pediatric drug development plan at the earliest possible time. The applicant submitted the Proposed Pediatric Study Request on September 28, 2001, to IND —— FDA 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 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 in pediatric population with chronic hepatitis B.

The applicant plans to initiate these studies in the second quarter of 2002.

10. Review of Financial Disclosure Information

Pursuant to 21 CFR Part 54, the covered clinical trials included the "pivotal" studies GS-98-437 and GS-98-438. Additionally, some data from study GS-98-435 were also relied on to establish that the drug is effective in patients with lamivudine-resistant HBV. Therefore, this study also appears to meet the definition of "covered clinical study."

The financial disclosure information of 354 investigators in study GS-98-437, 105 investigators in study GS-98-438, and 218 investigators (including principal and subinvestigators) in study GS-98-435 is presented in Table 10.

Table 10. Summary of Financial Disclosure Information

Requirement per 21 CFR §54(a)(3)(i)	GS-98-437	GS-98-438	GS-98-435
Number of investigators	354	105	218
No financial interest/arrangement	324	103	140
No information due to:			
Not enrolling patients	8		
Resigned prior to study completion	19	1	9
Did not complete information	1	1	58
Information not completely provided	-	-	11

Based on the disclosed information, it appears that the applicant has acted with due diligence to obtain the required information. None of the investigators in the "pivotal"studies GS-98-437 and GS-98-438 had any financial interests that raise a serious question about the integrity of the data. While the information in study GS-98-435 is incomplete, none of the investigators who have not submitted financial disclosure statement enrolled a substantial number of patients that would potentially compromise the data integrity.

11. Clinical Inspection

Five clinical sites (two in Greece and one each in Taiwan, Miami, and Pasadena) were inspected by the Division of Scientific Investigation, FDA (please see Memorandum from Antoine El-Hage, PhD, Associate Director, Division of Scientific Investigator to DAVDP dated August 16, 2002). The inspectors did not find "objectionable conditions" that would preclude the use of the data submitted to support the NDA.

12. Antiviral Drug Advisory Committee

An Antiviral Drug Advisory Committee meeting was held on August 6, 2002. Based on the favorable risk-benefit determination, the Committee voted unanimously to recommend approval of adefovir for the treatment of chronic hepatitis B in patients with active liver disease. Nevertheless, the Committee was concerned about the exacerbation of hepatitis associated with treatment discontinuation, treatment-emergent nephrotoxicity in patients with underlying renal dysfunction, and the lack of long-term resistance data. For complete information, please see the transcript of the proceeding.

13. Labeling Review

Labeling discussion with the applicant is in progress at the time this review is completed. A Patient Information insert is also under review by the Division of Surveillance, research, and Communication Support, FDA.

14. Conclusions

The benefits of adefovir treatment (see section 7.5) outweigh the identifiable risks associated with this drug (see section 8.9) as summarized below.

- Two adequate and well-controlled clinical studies in patients with compensated chronic hepatitis B established statistically significant evidence that that the drug could suppress HBV replication, decrease liver inflammation as evidenced both histologically and biochemically, reverse liver fibrosis, and accelerate HBeAg seroconversion. One uncontrolled study in pre-and post-liver transplantation in patients with and without liver decompensation showed that the drug could suppress lamivudine-resistant HBV replication and resulted in measurable clinical benefits.

- Most clinical adverse events and laboratory abnormalities associated with the drug were comparable to those seen in the placebo group. Nevertheless, there are two major safety issues with this drug. While treatment with the drug reduced the incidence of hepatic flare, discontinuation of the drug has been associated with acute exacerbation of the disease in a significant proportion of patients. Treatment-emergent nephrotoxicity is also of clinical concern. Although the risk of nephrotoxicity risk is low in patients with adequate renal function, the risk is significantly higher in patients with underlying renal dysfunction. Therefore, patients should be closely monitored for these adverse events. Dosing of the drug should be adjusted in patients with renal dysfunction. However, the safety and effectiveness of a proposed dose adjustment scheme has not been clinically established.

15. Recommendations

Based on the risk-benefit profile and discussions by the Antiviral Drug Advisory Committee of August 6, 2002, it is recommended that adefovir 10 mg daily dose be

approved for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B as follows:

- The indication of this drug should be for adult patients with evidence of active HBV replication by an HBV DNA assay and one of the following criteria: (1) histologic evidence of active disease (i.e., presence of interfaced hepatitis and bridging necrosis); or (2) laboratory evidence of persistent elevations of serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).

- The label should specifically and prominently address the following risks: (1) potentially severe exacerbation of hepatitis associated with treatment discontinuation; (2) treatment-emergent nephrotoxicity, particularly in patients at risk for or with underlying renal dysfunction. The label should also address the need to closely monitor patients for these adverse events.

- The label should contain the suggested dose adjustment of adefovir for patients with underlying renal dysfunction, with the qualification that the safety and effectiveness of which have not been established clinically.

- The label should state that the optimal duration of treatment and the long-term outcomes such as development of decompensated liver disease or hepatocellular carcinoma are not known.

Additional recommendations from other reviewing disciplines should also be considered.

Respectfully submitted,

/S/

Tan T. Nguyen, MD, PhD
Medical Reviewer
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