Pharmacokinetics of Adefovir after Oral Administration of Adefovir Dipivoxil 10 mg in Healthy Japanese Males and Japanese Patients with Chronic Hepatitis B

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The pharmacokinetics of adefovir dipivoxil, a novel reverse transcriptase inhibitor for the treatment of chronic hepatitis B, were investigated in healthy Japanese subjects (n=12) and Japanese patients with chronic hepatitis B (n=11).

Healthy males received single and multiple doses (once daily for 5 days) of adefovir dipivoxil 10 mg. After the first and final doses, blood and urine samples were collected over 48 hours and concentrations of adefovir, the hydrolysed active metabolite, measured by LC-MS/MS. Adefovir pharmacokinetic parameters (mean±SD) were comparable after single and multiple dosing: C_{max} 22.9 ± 3.3 and 24.5 ± 3.8 ng/mL, respectively. The single dose $AUC_{0-\infty}$ (239.4 ± 35.7 ng·hr/mL) and half-life (6.89 ± 1.21 hr) were also similar to AUC_{0-24} (249.3 ± 32.9 ng·hr/mL) and $t_{1/2}$ (7.73 ± 0.73 hr) after multiple dosing. The steady-state accumulation ratio was 1.05 ± 0.12 , indicating a lack of appreciable accumulation during multiple dosing. Approximately 60% of the dose was recovered in urine as adefovir.

Chronic hepatitis B patients with evidence of abnormal liver function associated with YMDD mutant hepatitis B virus and taking lamivudine 100 mg once daily were also studied. The results were similar to those in healthy subjects. C_{max} and $AUC_{0-\infty}$ after the first dose of adefovir dipivoxil 10 mg in chronic hepatitis B patients were 20.1 ± 3.3 ng/mL and 272.8 ± 51.3 ng·hr/mL, respectively. Furthermore, the pharmacokinetics of adefovir were comparable in patients with and without cirrhosis. Adefovir pharmacokinetics in Japanese subjects with normal renal function are therefore not altered by chronic hepatitis B infection, lamivudine co-administration or the severity of hepatic disease. These Japanese results are consistent with those in Western subjects and a major inter-ethnic difference is not observed.

Key words : adefovir dipivoxil, adefovir, pharmacokinetics, healthy male, hepatitis B

Introduction

Adefovir dipivoxil, a prodrug of the adenosine analogue adefovir (Fig.1), is a reverse transcriptase inhibitor that possesses broad spectrum antiviral activity against viruses such as hepadnaviruses, retroviruses and herpesviruses¹⁾. Currently, lamivudine (Zefix®) is widely used for the

treatment of chronic hepatitis B. However, long-term therapy with lamivudine is sometimes associated with the emergence of YMDD mutant hepatitis B virus, thereby resulting in hepatitis flares^{2,3)}. In this context, new therapies that are effective against YMDD mutant hepatitis B virus are needed. Adefovir dipivoxil at the recommended clinical dose of 10 mg/day is well tolerated and

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Fig. 1 Structural formula of adefovir dipivoxil

Chemical name : Bis (2,2-dimethylpropanoyloxymethyl) [2-(6-amino-9 H-purin-9-yl) ethoxymethyl] phosphonate

demonstrates excellent antiviral efficacy in chronic infection with hepatitis B virus, including the lamivudine-resistant YMDD mutant^{4,5}). Since 2002, adefovir dipivoxil (Hepsera®) has been used clinically in many countries worldwide including Europe, the United States (US), Canada and Australia. It was granted marketing approval in Japan in October 2004.

Following administration of adefovir dipivoxil it is rapidly hydrolysed to the active moiety, adefovir, and the pharmacokinetics of adefovir are therefore studied after administration of the prodrug. In the development program for adefovir dipivoxil in Japan, the pharmacokinetics of adefovir have been evaluated in two studies in Japanese subjects. The first study investigated the single and multiple dose pharmacokinetics of adefovir dipivoxil 10 mg in healthy adult male Japanese subjects. The second study investigated the pharmacokinetics of adefovir in Japanese patients with chronic hepatitis B following the first dose of a 16 week regimen of 10 mg adefovir dipivoxil and lamivudine 100 mg once daily. The Japanese patients with chronic hepatitis B had evidence of abnormal liver function associated with YMDD mutant hepatitis B virus replication while receiving lamivudine 100 mg.

This paper presents the results of these two studies in Japanese subjects. The single and multiple dose adefovir pharmacokinetics are compared in healthy subjects and the potential influence of chronic hepatitis B infection and its severity is also assessed.

Methods

Two studies investigating adefovir pharmacokinetics were performed. Written informed consent was obtained from all subjects and each study was approved by the relevant local Institutional Review Board in Japan. Both studies were conducted in accordance with the Declaration of Helsinki (South Africa, 1996) and Good Clinical Practice (GCP).

The first study investigated the pharmacokinetics of single and multiple dose adefovir in 12 Japanese male subjects considered healthy on the basis of medical history, vital signs, clinical laboratory tests or other examinations and had normal renal function. Demographic data of the subjects are summarised in Table 1. On Day 1 a single dose of adefovir dipivoxil 10 mg (Hepsera®, Gilead Sciences Inc, US) was administered. Blood samples (5 mL) for the analysis of adefovir in plasma were taken pre-dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose. On Day 4 once daily dosing with adefovir dipivoxil 10 mg was commenced for 5 days (Days 4-8). Pre-dose blood samples were taken on Days 4-7 to measure trough concentrations and on Day 8 blood samples were taken before the final dose and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose. All urine voided for 48 hours after administration of adefovir dipivoxil on Day 1 (single dose) and Day 8 (multiple dose) was collected to measure the amount of adefovir excreted in the urine. Adefovir dipivoxil was administered after an overnight fast on Day 1 and Day 8, but was administered in the fed state on Days 4-7. All doses of adefovir dipivoxil were administered with 150 mL water. The study design also included an additional 6 subjects who were randomised to receive placebo tablets. It was therefore conducted in a double blind manner. As the subjects administered placebo did not contribute information on the pharmacokinetics of adefovir, they have not been included in this report.

The second study investigated the pharmacokinetics of adefovir in 11 Japanese patients with chronic hepatitis B. These subjects were a subset of the 36 patients enrolled in an open label, uncontrolled 16 week multicentre study of the efficacy and safety of adefovir dipivoxil 10 mg once daily

Table 1 Subject demographics

Japanese subjects	Demographics of subjects included in pharmacokinetic analysis						
	No. of subjects	Demographics	Liver function			Renal function CL _{cr} (mL/min) ^{a)}	
Healthy	n=12	Male=12 Age ^{b)} : 25.5±5.1 (21-35) BW (kg) ^{b)} : 63.8±4.8 (56.6-72.2)	Normal ; ALT, AST, ALP, LDH and γ -GTP are below the upper limit of normal range			81-126.6	
Chronic hepatitis B patients who have evidence of abnormal liver function associated with YMDD mutant HBV replication	n=11	Male/Female=9/2, Hepatitis/Cirrhosis=7/4 Age ^{b)} : 45.5±7.2 (30-58), BW (kg) ^{b)} : 69.7±11.6 (54-89)	Diagnosis	Child-Pugh score ^{d)}	ALT (U/L)	Fibrosis score ^{e)}	97.8-226.2
			Hepatitis	5-6	48-678	F : 0-3	
			Cirrhosis ^{c)}	5-7	102-977	F : 4	

^{a)}: derived from Cockcroft-Gault equation; range

^{b)}: mean±SD (range)

^{c)}: cirrhosis diagnosed by liver biopsy/laparoscopy or by comprehensive diagnosis including diagnostic imaging

^{d)}: range of Child-Pugh scores, assessed in accordance with 'Criteria for Child-Pugh Classification'⁶⁾

^{e)}: range of Fibrosis scores, assessed in accordance with the 'Knodel Score'⁷⁾

with lamivudine 100 mg. All subjects had evidence of abnormal liver function associated with YMDD mutant hepatitis B virus replication, compensated liver function and normal renal function and were taking lamivudine 100 mg once daily. Demographic data of the patients are summarised in Table 1^{6,7)}. Two of the 11 subjects were female. Women have been included in studies in the West and no gender differences in adefovir pharmacokinetics have been reported⁸⁾. Four of the 11 subjects with chronic hepatitis B were also diagnosed with cirrhosis.

The 11 subjects with chronic hepatitis B were studied following the first dose of the once daily adefovir dipivoxil 10 mg with concomitant administration of lamivudine 100 mg regimen. Blood samples (5 mL) for the measurement of adefovir plasma concentrations were collected pre-dose and at 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose. Adefovir dipivoxil was administered with 150 mL water and all subjects were fasted at dosing.

Plasma and urine concentrations of adefovir were determined at Takasaki Research Laboratories, GlaxoSmithKline (Japan) using a validated liquid chromatography mass spectrometry (LC-MS/MS) method. The within and between coefficients of variation of the precision of these methods were less than 13.07% and the accuracies* were ±12.93%. The lower limit of quantification (LLQ) was 1.00 ng/mL for plasma adefovir and 50.0 ng/

mL for adefovir concentrations in urine.

$$* : \frac{\text{Mean measured concentration} - \text{Nominal concentration}}{\text{Nominal concentration} \times 100}$$

Adefovir pharmacokinetic parameters including C_{max}, t_{max}, t_{1/2}, AUC₀₋₂₄, AUC_{0-∞} and CL/F were calculated using standard noncompartmental techniques and WinNonlin Professional Version 3.1 (Pharsight Corp, Mountain View CA, US). AUC was calculated using the log-linear trapezoidal rule. The amount of adefovir recovered in the urine (Ae) and the fraction of the adefovir dose excreted in the urine (fe) were calculated from the urine volume voided and adefovir concentration measured for each sampling period, with cumulative 0-48 hour data being considered for the single dose of adefovir and the 24 hour dosing interval being considered for multiple dosing. Adefovir renal clearance (CL_R) after a single dose was calculated as Ae₀₋₄₈/AUC₀₋₄₈ and after multiple dosing as Ae₀₋₂₄/AUC₀₋₂₄. The accumulation ratio, Ro, was calculated as AUC₀₋₂₄ (multiple dosing)/AUC₀₋₂₄ (single dose) and Rs was calculated as AUC₀₋₂₄ (multiple dosing)/AUC_{0-∞} (single dose).

All data including pharmacokinetic parameters are reported as arithmetic mean±SD, with the exception of t_{max} which is presented as the median and range.

Results

The plasma adefovir concentration-time profiles following single and multiple doses of adefovir dipivoxil 10 mg in healthy Japanese subjects are shown in Figure 2. The adefovir pharmacokinetic parameters calculated in these subjects are given in Table 2.

The pharmacokinetic parameters of adefovir in Japanese subjects were comparable following sin-

Fig. 2 Single and multiple dose plasma adefovir concentration-time profiles in healthy Japanese subjects (mean $\pm$ SD, $n=12$)

The arrows represent the time of administration of an oral dose of 10 mg adefovir dipivoxil. The pre-dose concentrations during multiple dosing are also shown. The axis breaks signify a change in the scale of the time axis.

gle (Day 1) and 5 days multiple dosing (Day 8) of adefovir dipivoxil. Adefovir C_{max} after single and 5 days multiple dosing occurred at 0.75 and 1.00 hours, respectively, indicating rapid absorption. Adefovir was eliminated from plasma with $t_{1/2}$ of 6.89 ± 1.21 and 7.73 ± 0.73 hours follow single and repeat dose administration, respectively. The accumulation ratio, R_o , was 1.16 ± 0.11 and R_s was 1.05 ± 0.12 . This indicates the lack of appreciable accumulation of adefovir after once daily dosing of adefovir dipivoxil 10 mg, and that adefovir pharmacokinetics are not altered during multiple dosing. The lack of appreciable accumulation is consistent with the half-life of adefovir observed. Trough (pre-dose) adefovir plasma concentrations were also measured during multiple dosing of adefovir dipivoxil and are shown in Figure 2. The trough concentrations of adefovir observed during multiple dosing indicate that steady-state was attained after about 3 days of multiple once daily dosing.

Approximately 60% of the administered dose of adefovir was excreted in the urine by 48 hours after a single dose and over the 24 hour dosing interval during multiple dosing. Western studies have shown that following administration of adefovir dipivoxil, adefovir is excreted predominantly via the kidney and that renal tubular secretion contributes to the renal clearance of adefovir^{9,15}. The oral bioavailability of adefovir has been estimated to be approximately 59%⁸. The urinary recovery of adefovir in Japanese subjects is consistent with the bioavailability and renal recovery observed in Western subjects.

Table 2 Adefovir pharmacokinetic parameters following single and multiple dose administration of adefovir dipivoxil 10 mg in healthy Japanese subjects, and following the first 10 mg adefovir dipivoxil dose in Japanese patients with chronic hepatitis B

Subjects (n)	Dosing	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	CL _R (L/hr)	fe (%)
Healthy subjects (12)	Single dose	22.9 ± 3.3 (18.2-29.5)	0.75 (0.50-1.00)	239.4 ± 35.7 (179.9-295.1)	215.5 ± 30.4 (171.6-266.3)	6.89 ± 1.21 (5.20-8.90)	23.2 ± 3.6 (18.5-30.3)	14.1 ± 2.3 (10.6-18.7)	$60.8 \pm 12.3^a)$ (43.4-86.8)
	Day 5 of dosing	24.5 ± 3.8 (16.2-29.6)	1.00 (0.50-3.00)	—	249.3 ± 32.9 (214.2-326.8)	7.73 ± 0.73 (6.52-8.88)	19.4 ± 2.3 (15.0-22.5)	$12.9 \pm 2.5^b)$ (8.2-18.0)	$59.5 \pm 12.4^{b,c)}$ (34.3-75.3)
Chronic hepatitis B patients (11)	First dose ^{d)}	20.1 ± 3.3 (15.3-27.6)	1.00 (0.50-2.00)	$272.8 \pm 51.3^e)$ (211.5-337.5)	$231.5 \pm 33.7^e)$ (185.8-275.4)	$8.23 \pm 2.05^e)$ (5.87-12.8)	$20.6 \pm 3.9^e)$ (16.1-25.8)	NA ^{f)}	NA ^{f)}

Parameters are given as mean $\pm$ SD (range), except t_{max} which is given as median (range).

^{a)}: fe_{0-48} , ^{b)}: $n=11$, ^{c)}: fe_{0-24} , ^{d)}: combination therapy with lamivudine, ^{e)}: $n=10$, ^{f)}: not available

The adefovir plasma concentration-time profile in Japanese chronic hepatitis B patients following the first dose of 10 mg adefovir dipivoxil is shown in Figure 3 and compared with that observed in healthy Japanese subjects following a single dose of adefovir dipivoxil 10 mg. The two populations showed a similar profile in that the maximum plasma concentrations were achieved at approximately 1 hour post-dose and then declined to levels of 2–3 ng/mL at 24 hours post-dose. Of note, the extrapolated area under the curve between $AUC_{0-1\text{st}}$ and $AUC_{0-\infty}$ ranged from 7.1% to 27.5% (mean <15%) in the chronic hepatitis B patients. This is only slightly greater than that observed in healthy subjects (3.2 to 11.6%, mean <7%).

The adefovir pharmacokinetic parameters observed in the Japanese patients with chronic hepatitis B are given in Table 2. Adefovir C_{max} (20.1 ± 3.3 ng/mL) and $AUC_{0-\infty}$ (272.8 ± 51.3 ng·hr/mL) in Japanese chronic hepatitis B patients were similar to the values observed in healthy Japanese subjects (Table 2). The ranges of individual values for both parameters were also similar in the healthy subjects and patients with chronic hepatitis B. The elimination half-life of adefovir in chronic hepatitis B patients was 8.23 ± 2.05 hr. This value was slightly longer than for healthy subjects (6.89 ± 1.21 hr), but there was considerable overlap between the two populations in the range of individual values observed. CL_R was not calculated in the chronic hepatitis B patients, but CL/F values were similar to healthy subjects.

Four of the 11 patients with chronic hepatitis B were also diagnosed with cirrhosis and therefore

had more advanced liver disease (Fibrosis score, F:4) (Table 1). For this reason, the C_{max} and $AUC_{0-\infty}$ values were also summarised by diagnosis (hepatitis alone or additional cirrhosis) and then compared with those observed in healthy subjects. As presented in Figure 4, the adefovir C_{max} and $AUC_{0-\infty}$ were similar in Japanese chronic hepatitis B patients with and without additional cirrhosis and were also similar to those in healthy Japanese subjects. The pharmacokinetics of adefovir in Japanese patients with normal renal function are therefore unlikely to be altered by the presence or severity of chronic hepatitis B infection.

No serious or severe adverse events were reported and adefovir dipivoxil 10 mg was well tolerated

Fig. 3 Adefovir plasma concentration-time profiles in Japanese subjects following a single 10 mg dose of adefovir dipivoxil (mean $\pm$ SD). For chronic hepatitis B patients $n=10$ at 24 hours post-dose.

Fig. 4 Adefovir C_{max} and $AUC_{0-\infty}$ following administration of 10 mg adefovir dipivoxil to Japanese patients with chronic hepatitis B alone (C_{max} : $n=7$, $AUC_{0-\infty}$: $n=6$) or with additional cirrhosis ($n=4$) and to healthy Japanese subjects ($n=12$)

in the Japanese subjects studied. In the healthy subjects after both single and multiple dosing all adverse events were mild in intensity and no adefovir dipivoxil-related adverse events were observed. After sixteen weeks of combination therapy with lamivudine, all drug related adverse events reported in the patients with chronic hepatitis B were also of mild intensity and the events were mostly similar to those reported for lamivudine in Japanese subjects or for adefovir dipivoxil in overseas studies.

Discussion

In vitro studies indicate that adefovir dipivoxil is metabolised to adefovir by carboxyesterases¹⁰⁾ and that adefovir dipivoxil is rapidly converted to adefovir in human serum with $t_{1/2}$ of <5 minutes¹¹⁾. It is expected that orally administered adefovir dipivoxil undergoes rapid hydrolysis *in vivo* by esterases in the small intestine and blood yielding adefovir¹²⁾. The rapid attainment of maximum adefovir plasma concentrations (t_{max} <1 hour) is consistent with rapid hydrolysis *in vivo*. Adefovir displays linear pharmacokinetics^{9,13,14)} and has negligible plasma protein binding ($\leq 4\%$)¹⁵⁾. The estimated oral bioavailability of adefovir from adefovir dipivoxil is approximately 59%⁸⁾ and administration with food has no notable effect on adefovir pharmacokinetics¹⁶⁾. The primary route of

elimination of adefovir is via the kidney and adefovir is considered to be excreted by both glomerular filtration and renal tubular secretion^{9,15)}. Adefovir has been reported to interact with a number of transport proteins which are expressed in the kidney including OAT 1¹⁷⁾ and MRP 2¹⁸⁾. Renal function is therefore the major factor affecting adefovir elimination and therefore pharmacokinetics.

The pharmacokinetic profile of adefovir in healthy adult male Japanese subjects was similar following single and multiple dose administration (Fig. 2). Consistent with data in Western subjects¹⁶⁾, the Japanese studies indicate that the pharmacokinetics of adefovir are unchanged during once daily dosing of adefovir dipivoxil 10 mg and that adefovir does not accumulate appreciably during chronic administration.

The pharmacokinetic parameters of adefovir in healthy Japanese subjects could also be compared with those in Japanese chronic hepatitis B patients. The pharmacokinetics of adefovir following the first dose of adefovir dipivoxil 10 mg in Japanese patients with compensated chronic hepatitis B taking lamivudine were similar to those observed in healthy subjects given a single dose of adefovir dipivoxil 10 mg. The steady-state pharmacokinetics of adefovir in healthy Japanese subjects and Japanese patients with chronic hepatitis B are

Table 3 Summary of adefovir pharmacokinetics characteristics

Absorption	-Adefovir displays linear pharmacokinetics ^{9,13,14)} . -The estimated oral bioavailability of adefovir is approximately 59% ⁸⁾ . -No notable effect of food on adefovir pharmacokinetics ¹⁶⁾ .
Distribution	-Binding of adefovir to human plasma or serum proteins is $\leq 4\%$ ¹⁵⁾ .
Metabolism	-Adefovir dipivoxil is metabolised to adefovir by carboxyesterases ¹⁰⁾ . -Adefovir dipivoxil is rapidly converted to adefovir in human serum with $t_{1/2}$ of <5 minutes ¹¹⁾ . -Adefovir dipivoxil is rapidly hydrolysed to adefovir by esterases in the small intestine or blood ^{11,12)} .
Elimination	-Adefovir is renally excreted by a combination of glomerular filtration and renal tubular secretion ^{9,15)} . -Adefovir interacts with a number of transport proteins which are expressed in the kidney including OAT1 and MRP2 ^{17,18)} .
Profile of clinical pharmacokinetics	-The pharmacokinetic profile of adefovir is similar following single and multiple dose administration ¹⁶⁾ . -The pharmacokinetics of adefovir are similar in healthy subjects and patients with chronic hepatitis B ¹⁶⁾ . -Adefovir pharmacokinetics are similar in men and women ⁸⁾ . -Adefovir exposure is increased in patients with renal impairment and modified dosing regimens are necessary if CL_{cr} < 50 mL/min ²²⁾ . -Adefovir pharmacokinetics are not influenced by hepatic impairment and no need to change the dosage regimen ¹⁹⁾ .
Drug interaction	-Adefovir dipivoxil does not interact with lamivudine, acetaminophen and trimethoprim/sulfamethoxazole ²⁰⁾ . -Adefovir C_{max} (33%), AUC (23%) and urinary recovery are increased when co-administered with ibuprofen ²⁰⁾ .

therefore also anticipated to be comparable. In addition, the pharmacokinetics are similar in Japanese chronic hepatitis B patients with (F : 4) and without (F : 0-3) cirrhosis, consistent with data in Western patients with hepatic impairment (Child-Pugh score of 7-9 and >9)¹⁹⁾. Therefore, the steady-state pharmacokinetics of adefovir in Japanese patients with normal renal function are unlikely to be altered by the presence or severity of chronic hepatitis B.

Furthermore, in healthy Japanese subjects the pharmacokinetics of adefovir after adefovir dipivoxil alone are comparable to those in Japanese chronic hepatitis B patients also taking lamivudine. Previous studies in Western subjects have also reported that the pharmacokinetics of adefovir are similar in healthy subjects and patients with chronic hepatitis B¹⁶⁾ and that adefovir dipivoxil does not interact with lamivudine²⁰⁾. In Japanese patients with chronic hepatitis B we confirmed that the pharmacokinetics of adefovir are not altered by concurrent lamivudine administration.

The pharmacokinetics of adefovir in Western¹⁶⁾ and Chinese¹³⁾ subjects following administration of adefovir dipivoxil are consistent with the pharmacokinetics observed in this investigation in Japanese subjects (Table 2). In healthy Western and Chinese subjects and Western patients with chronic hepatitis B administered single oral doses of adefovir dipivoxil 10 mg, the adefovir C_{max} was reported as 20.4, 22.1 and 17.5 ng/mL, respectively. In these studies the $AUC_{0-\infty}$ was reported as 192, 235 and 210 ng·hr/mL, respectively^{13,16)}. The renal clearance of adefovir after a single oral dose of adefovir dipivoxil 10 mg has been reported to be 13.9 L/hr in healthy Western¹⁵⁾ subjects and 12.4 L/hr in Chinese subjects¹³⁾. The values of these pharmacokinetic parameters are generally consistent with the results from the two studies in Japanese subjects. A major inter-ethnic difference in the pharmacokinetics of adefovir between Japanese or Chinese and Western, predominantly Caucasian, subjects is therefore not observed. As adefovir is predominantly eliminated in the urine, these observations also indicate that the renal handling of adefovir is similar in Japanese, Chinese and Western subjects. This finding is consistent with the literature, as substantial inter-ethnic dif-

ferences in drug renal elimination have not been reported²¹⁾. Nevertheless renal impairment can influence the pharmacokinetics of adefovir as it is eliminated predominantly via renal excretion. Studies in Western subjects have demonstrated that patients with renal impairment have higher adefovir exposures following standard doses and that in these patients the dosing regimen should be adjusted²²⁾.

In conclusion, this investigation has characterised the single dose pharmacokinetics of adefovir in healthy Japanese subjects and Japanese patients with chronic hepatitis B. No influence of disease or concomitant lamivudine administration was observed. In addition in the healthy Japanese subjects the pharmacokinetics at steady-state following multiple dose administration were comparable to those observed after a single dose of adefovir dipivoxil 10 mg. Comparison with literature data suggest no major inter-ethnic difference in adefovir pharmacokinetics. The pharmacokinetics of adefovir administered as adefovir dipivoxil are affected by renal function. In patient populations with normal or near normal renal function, the effect of disease severity and ethnicity on adefovir pharmacokinetics is negligible.

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