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Adefovir Dipivoxil

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Contents

Abstract

▲ Adefovir dipivoxil is an ester prodrug of the nucleoside reverse transcriptase inhibitor adefovir (PMEA), the prototype compound of the acyclic nucleoside phosphonates. It has better oral bioavailability than the parent compound.

▲ Adefovir dipivoxil 120mg once daily significantly reduced viral load compared with placebo when added to standard antiretroviral therapy in a 6-month, double-blind study in patients with HIV infection. Viral suppression was maintained during an additional 6-month nonblind extension phase.

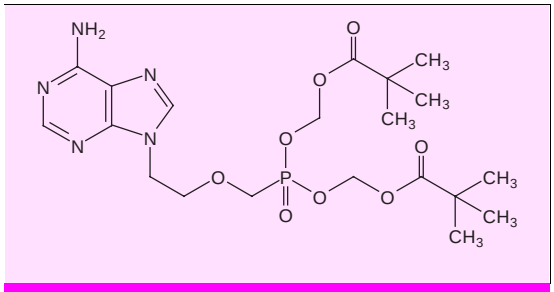
▲ The drug was most effective in patients with baseline isolates containing the M184V lamivudine resistance mutation according to data from a virological substudy of a large placebo-controlled trial.

▲ Adefovir dipivoxil 60mg was as effective as 120mg (both once daily) after 20 weeks' treatment in a randomised double-blind study in antiretroviral-experienced (protease inhibitor-naive) patients.

▲ Viral suppression was generally maintained in patients who developed new reverse transcriptase mutations during adefovir dipivoxil monotherapy or combination therapy for up to 12 months. No clear pattern of particular clinical resistance mutations has emerged.

▲ GI disturbances, hepatic effects and delayed renal abnormalities are the principal adverse events seen with adefovir dipivoxil. Reductions in serum free carnitine levels may occur and coadministration of L-carnitine is recommended.

Features and properties of adefovir dipivoxil (GS 840)	
Indications	
HIV infection (focus of this review)	
Cytomegalovirus infection	
Hepatitis B infection	
Mechanism of action	
Antiviral	DNA polymerase/reverse transcriptase inhibitor
Dosage and administration	
Usual dosage in clinical trials in HIV infection	60 or 120mg
Route of administration	Oral
Frequency of administration	Once daily
Additional requirement	L-carnitine 500 mg/day should be taken with adefovir dipivoxil to prevent reductions in serum carnitine levels
Pharmacokinetic profile of adefovir after oral administration of adefovir dipivoxil 125mg once daily for 14 days, unless stated otherwise	
Bioavailability	41% (with food); 30% (fasted) [500mg single dose]
Peak plasma concentration	0.24 mg/L
Time to peak plasma concentration	1.8h
Area under the plasma concentration-time curve	3.2 mg/L • h (250mg once daily for 14 days)
Elimination half-life	4.2h (250mg once daily for 14 days)
Adverse events	
Main events	GI disturbances, elevated hepatic enzyme levels, renal dysfunction



Adefovir dipivoxil

Adefovir dipivoxil (GS 840) is an ester prodrug of the nucleoside reverse transcriptase inhibitor adefovir [9-(2-phosphonylmethoxyethyl)adenine (PMEA)], the prototype compound of the acyclic nucleoside phosphonates (ANP) class. Unmodified adefovir has activity against retro-, herpes- and hepadnaviruses but, like other ANP analogues, displays poor oral bioavailability as a result of the highly anionic phosphonate moiety (which limits transport into intestinal cells). Ester derivatives of adefovir and other ANP analogues (with a lipophilic molecule added to the phosphonate group) have been synthesised to improve cellular uptake.

This New Drug Profile focuses on data pertinent to the use of adefovir dipivoxil in patients with HIV infection (see Naesens et al.[1] and Naesens & De Clercq[2] for information on the activity and clinical potential of this drug against other types of viral infection).

1. Pharmacodynamic Properties

Mechanism of Action

• Expression of the antiviral efficacy of adefovir dipivoxil requires hydrolysis to adefovir followed by phosphorylation to the active adefovir diphosphate moiety (reviewed by Balzarini[3] and Naesens et al.[1]). The diphosphate competitively inhibits deoxyadenosine triphosphate as a substrate for reverse transcriptase (inhibition constant for HIV-1 reverse transcriptase = 0.09 μmol/L)[4,5] and/or causes chain termination when incorporated into the growing DNA chain (reviewed by Balzarini[3]).

In Vitro Anti-HIV Activity and Cytotoxicity

This section focuses on the effects of unmodified adefovir (rather than adefovir dipivoxil) since the prodrug is rapidly converted to adefovir after oral administration (section 2).

• The concentration of adefovir required to inhibit replication of various HIV-1 strains by 50% (IC_{50}) in a number of T lymphocyte cell lines (MT-2, MT-4, CEM, C8166, ATH8, HeLa and H9) ranged from 0.4 to 30 μmol/L.[6-13] The adefovir IC_{50} was ≈0.02 μmol/L in monocytes/macrophages[7,8,12] or resting peripheral blood mononuclear cells,[14] and 2.5[12] or 3.7[7] μmol/L in peripheral blood lymphocytes.

• The concentration of adefovir which inhibited cell growth (for a range of T cell lines) by 50% ranged from 54 to 300 μmol/L.[6,7,9-13,15]

• The *in vitro* therapeutic (or selectivity) index [the ratio of cytotoxic to antiviral effects] for unmodified adefovir in a variety of T cell lines ranged from ≈2 to ≈200.[6,7,9-13,15]

• The potential for synergy between unmodified adefovir and other antiretroviral drugs in HIV_{IIIB}-infected MT-2 cells was investigated using 3-dimensional dose-response analysis.[9] Synergy was marked with the combination of adefovir and zidovudine, moderate with adefovir and didanosine, and minor when adefovir was combined with either 9-[(*R*)-2-(phosphonomethoxy)propyl]adenine monohydrate (PMPA; tenofovir), stavudine, nelfinavir, ritonavir or saquinavir. Combining adefovir with either zalcitabine, lamivudine or indinavir had additive effects. There was no evidence of antiviral antagonism for any adefovir combination.

• Unmodified adefovir combined with stavudine, zidovudine or saquinavir produced synergistic activity against $HIV\text{-}1_{IIIB}$ in MT-2 cells according to fractional inhibitory concentration analysis.[9] Additive effects were seen when adefovir was combined with indinavir.

Viral Resistance

In Vitro

• *In vitro* passaging of HIV in the presence of increasing concentrations of unmodified adefovir

produced 2 separate reverse transcriptase mutations [lysine to arginine at codon 65 (K65R) and lysine to glutamic acid at codon 70 (K70E)] associated with up to 15-fold resistance to adefovir.[16-18]

- The susceptibility to adefovir of HIV-1 isolates showing ≈50- to 200-fold resistance to zidovudine was reduced by approximately 2- to 8-fold compared with that of wild-type virus.[19] However, IC_{50} values for adefovir against a panel of HIV-1 isolates with intermediate resistance to zidovudine (≈8- to 25-fold decrease in susceptibility) were similar to those for adefovir against isolates from zidovudine-naive patients (0.7 to 1.7 *vs* 2 μmol/L).

- Susceptibility testing of recombinant viruses derived from zidovudine-resistant isolates with the M184V lamivudine resistance mutation showed that the latter mutation was associated with a 3- to 4-fold increase in sensitivity to adefovir.[20] The presence of the M184V mutation in zidovudine-sensitive isolates produced more variable effects on susceptibility to adefovir (ranging from no change to a 3-fold increase).

In Vivo

- In a phase I/II trial, new reverse transcriptase mutations potentially associated with adefovir dipivoxil therapy were detected in HIV isolates from 8 of 29 patients after 6 to 12 months of maintenance therapy with 120mg once daily (5 monotherapy and 3 combination therapy recipients). 15 patients received monotherapy for the first 6 months of maintenance treatment. Viral suppression was maintained in all patients with new mutations.[21] Of the 2 mutations identified *in vitro* after exposure to adefovir, the K70E substitution was seen in virus from 2 patients (1 each for monotherapy or combination therapy).

- The K70E and K65R mutations were not detected in viral isolates from 142 patients who received adefovir dipivoxil 120mg once daily or placebo for 24 weeks in addition to existing antiretroviral therapy in a phase II/III trial.[22]

Immunomodulatory Effects

- Adefovir significantly enhanced natural killer (NK) cell activity and interferon (IFN) α/β production when administered intraperitoneally once daily for up to 5 days in C57BL/6 mice (compared with untreated controls).[23,24] IFN is well known as an inducer of NK cell activity; although there was some evidence of a correlation between enhancement of NK cell activity and increased IFN levels during repeated administration,[24] this relationship was not universal across all dose levels and different durations of drug administration.

2. Pharmacokinetic Properties

Most of the data cited in this section relate to the pharmacokinetics of adefovir after administration of adefovir dipivoxil, supplemented where necessary with results from studies that administered unmodified adefovir. The pharmacokinetics of unmodified adefovir have been described in animals and in patients with HIV infection.[11,25-28]

Absorption and Distribution

- Adefovir dipivoxil diffuses passively into cells, unlike adefovir, which appears to require an endocytosis-like transport process.[29,30] The intestinal permeability of adefovir is enhanced when the drug is provided as adefovir dipivoxil rather than free adefovir. The *in vitro* permeability of adefovir dipivoxil across Caco-2 intestinal mucosal monolayers was 7.9×10^{-6} compared with 1.0×10^{-6} cm/sec for unmodified adefovir.[31] In a similar *in vitro* study, 8.8% of available adefovir dipivoxil was transported across Caco-2 intestinal mucosal monolayers after 3 hours, compared with <0.1% (below the level of detection) for unmodified adefovir.[32]

- Metabolic studies of radiolabelled adefovir dipivoxil and adefovir in MT-2 cells revealed a >100-fold increase in cellular uptake of the prodrug compared with the parent drug.[13]

- Results from *in vitro*[32] and *in vivo* animal[27,33,34] studies suggest that adefovir dipivoxil is rapidly and completely hydrolysed to the monoester metabolite and to adefovir. Adefovir dipivoxil was not

detected in the plasma of mice or monkeys after single-dose oral administration.[33,34]

- In mice, the bioavailability and area under the plasma concentration-time curve (AUC) of adefovir were 3.3- and 4.4-fold greater after single-dose oral administration of adefovir dipivoxil (equivalent to adefovir 50 mg/kg) than after administration of unmodified adefovir (50 mg/kg) [52.8 *vs* 15.9% and 823 vs 185 mg/L · h].[33]).

- The bioavailability of adefovir after once-daily oral administration of adefovir dipivoxil 125 to 500mg was estimated as ≈32 to 45% (measured on day 1 or day 14, relative to previous data for intravenous administration of adefovir) in 27 patients with HIV infection.[35] The oral biovailability of adefovir after administration of the unmodified drug in patients with HIV infection was <12%.[26]

- Absorption of adefovir after oral administration of the prodrug was generally dose proportional, as assessed by peak plasma concentrations (C_{max}) and AUC on days 1 and 14 of once-daily treatment with 125, 250 and 500mg in 27 patients with HIV infection.[35] C_{max} for the 125mg group (0.24 mg/L) was reached after 1.8 hours. AUC for the 250mg group (125mg not determined) was 3.2 mg/L · h.

- Administration of single-dose oral adefovir dipivoxil 500mg with food significantly increased bioavailability of adefovir compared with that for administration in a fasted state (41 *vs* 30%, p = 0.004) in 10 patients with HIV infection.[36] Bioavailability was calculated relative to historical AUC data for intravenous adefovir 1 mg/kg.

- Protein binding of adefovir in human plasma or serum was negligible (<3%) over the concentration range 0.25 to 25.0 μmol/L (0.125 to 12.5 mg/L).[26] The steady-state volume of distribution of adefovir in patients who received intravenous adefovir 1 or 3 mg/kg was 0.42 L/kg.[26]

Elimination

- Total serum clearance of adefovir approximated renal clearance (223 vs 205 ml/h/kg) after intravenous administration of adefovir 1 or 3 mg/kg to 28 patients with HIV infection.[26] Renal clearance of adefovir was significantly greater than baseline creatinine clearance, indicating that the drug is subject to active tubular secretion.

- In patients with HIV infection who received adefovir dipivoxil 250mg (n = 9) or 500mg (n = 9) once daily for 14 days, the terminal elimination half-life of adefovir was 4.2 or 5.8 hours.

- Adefovir is excreted predominantly as the unchanged drug. Urinary recovery of adefovir after 14 days' administration of adefovir dipivoxil 125, 250 or 500mg was 41, 31 or 28%[35] (which approximates to oral bioavailability). 98% of an intravenous dose of adefovir was recovered unchanged in the urine of patients with HIV infection.[26]

- The intracellular half-life of adefovir diphosphate in a T lymphocyte cell line (MT-4) was 16 to 18 hours.[5]

3. Clinical Efficacy

The efficacy of adefovir dipivoxil was first demonstrated in a small placebo-controlled monotherapy trial.[37] Subsequent studies have used adefovir dipivoxil as part of combination regimens (in line with accepted clinical practice), mainly in previously treated patients with HIV infection.

Comparison with Placebo

- Adefovir dipivoxil 120mg once daily significantly reduced viral load compared with placebo when used in addition to standard antiretroviral therapy in a randomised, double-blind multicentre phase II/III study in 442 antiretroviral-experienced patients [study GS408].[38,39] Most patients (93%) were receiving combination therapy at baseline. After 6 months' treatment, the mean reduction from baseline in plasma HIV RNA level was ≈0.4 $\log_{10}$ copies/ml in adefovir dipivoxil recipients, whereas viral load was unchanged in placebo recipients ($p < 0.0001$; intent-to-treat analysis). Adefovir dipivoxil-treated patients were ≈3 times more likely than placebo recipients to have a viral RNA level below 500 copies/ml (fig. 1) [statistical analysis not reported].

- In an extension phase of the GS408 trial, the level of viral suppression seen after 6 months' treat-

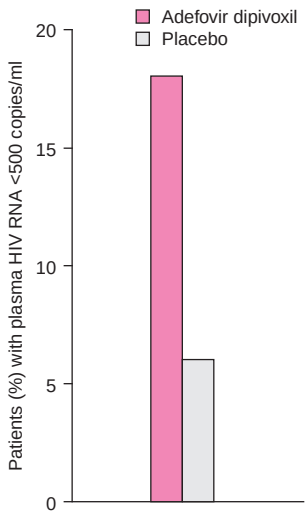


Fig. 1. Suppression of plasma HIV RNA with adefovir dipivoxil when added to existing antiretroviral therapy in patients with HIV infection.[38,39] 442 patients received adefovir dipivoxil 120mg or placebo once daily for 6 months in addition to existing antiretroviral therapy in a randomised, double-blind, multicentre study. Baseline status: mean CD4+ count = 352 cells/μl; mean HIV RNA level = 4.4 log10 copies/ml. Statistical analysis not provided.

ment with adefovir dipivoxil was maintained after a further 6 months' nonblind therapy.[38] In patients who had previously received placebo, median HIV RNA level at the end of the extension phase was ≈0.45 $\log_{10}$ units lower than after the initial 6-month treatment phase (n = 142).

• Adefovir dipivoxil significantly reduced plasma HIV RNA levels compared with placebo in patients with viral isolates containing the lamivudine-associated M184V mutation (with or without mutations associated with zidovudine resistance)[38] [fig. 2] according to data from a prospective virological substudy of the GS408 trial (n = 142). A nonsignificant difference in favour of adefovir dipivoxil over placebo was evident for patients with baseline isolates with low level zidovudine resistance mutations but not the M184V mutation. Patients whose baseline isolates had high level zidovudine resistance mutations without the M184V mutation did not appear to respond to treatment.

• Data from the GS408 virological substudy showed that viral suppression was maintained in patients with isolates that developed new mutations during treatment with adefovir dipivoxil and existing antiretroviral drugs (mean change from baseline in plasma HIV RNA –0.64 *vs* –0.01 $\log_{10}$ copies/ml with placebo, p = 0.0003).[22]

Dosage Comparison

• Once-daily treatment with adefovir dipivoxil 60mg was as effective as 120mg once daily in a randomised double-blind study in 211 patients who had previously received nucleoside reverse transcriptase inhibitors but not protease inhibitors.[40] After 20 weeks, the difference between the 2 groups in the percentage of patients with HIV RNA levels below 400 copies/ml (primary end-point) was not statistically significant (fig. 3; absolute difference 9%, 95% confidence interval of difference = –4.3 to 22.1%). Mean change from baseline in plasma HIV RNA level at 20 weeks was ≈1.25 $\log_{10}$ copies/ml in both groups; mean increase in CD4+ counts was ≈85 and ≈75 cells/μl for 60 and 120mg.

Other Studies

• Interim data from 114 of 221 antiretroviral therapy-naive patients enrolled in a randomised nonblind study suggest that combinations of adefovir dipivoxil 120mg once daily and indinavir plus either zidovudine, lamivudine, stavudine or lamivudine plus zidovudine (dosages not reported) are as effective as standard triple therapy with zidovudine, lamivudine and indinavir after 20 weeks' treatment.[41] Median reduction in plasma HIV RNA level was 2.12 to 2.51 $\log_{10}$ copies/ml for adefovir-containing groups and 2.15 $\log_{10}$ copies/ml for standard triple therapy.

• Adefovir dipivoxil 1.5 mg/kg plus existing antiretroviral therapy and nelfinavir (from day 7) reduced viral load by 1.34 $\log_{10}$ copies/ml from baseline in 16 paediatric patients (aged 4 months to 16 years) who were treated for 4 weeks (interim analysis).[42]

4. Tolerability

• Individual and pooled data from clinical trials indicate that GI disturbances, asymptomatic elevations in hepatic enzyme levels and nephrotoxicity (elevated serum creatinine levels, hypophosphataemia) are the major adverse events associated with adefovir dipivoxil therapy.[35,37,38,40,43]

• Reductions in serum free carnitine levels may occur during adefovir dipivoxil therapy [e.g. a 42% reduction from baseline in mean level after 12 weeks in a monotherapy study (n = 24)[37]] and coadministration of L-carnitine (500 mg/day) is recommended.[44] However, no clinical sequelae related to this effect have been demonstrated after adefovir dipivoxil therapy.

• Grade 3 or 4 or serious treatment-related adverse events occurred in ≈12% of 1300 patients enrolled in phase II/III clinical trials [of whom ≈900 received adefovir dipivoxil (dosage not reported)], according to retrospective analysis.[43] 450 patients were treated for >6 months. Most events (68%) were asymptomatic laboratory abnormalities. Elevations in AST or ALT were detected in ≈5% of patients. About 1.5% of patients experienced renal abnormalities; about half of these patients had proximal tubular defects with bicarbonate and phosphate wasting, proteinuria and glucosuria, with or without increases in serum creatinine levels. Elevation of serum creatinine to >2.0 mg/dl (>177 μmol/L) occurred in 12 patients.

• Only 2% of 5640 patients receiving adefovir dipivoxil (plus other antiretrovirals) as part of the

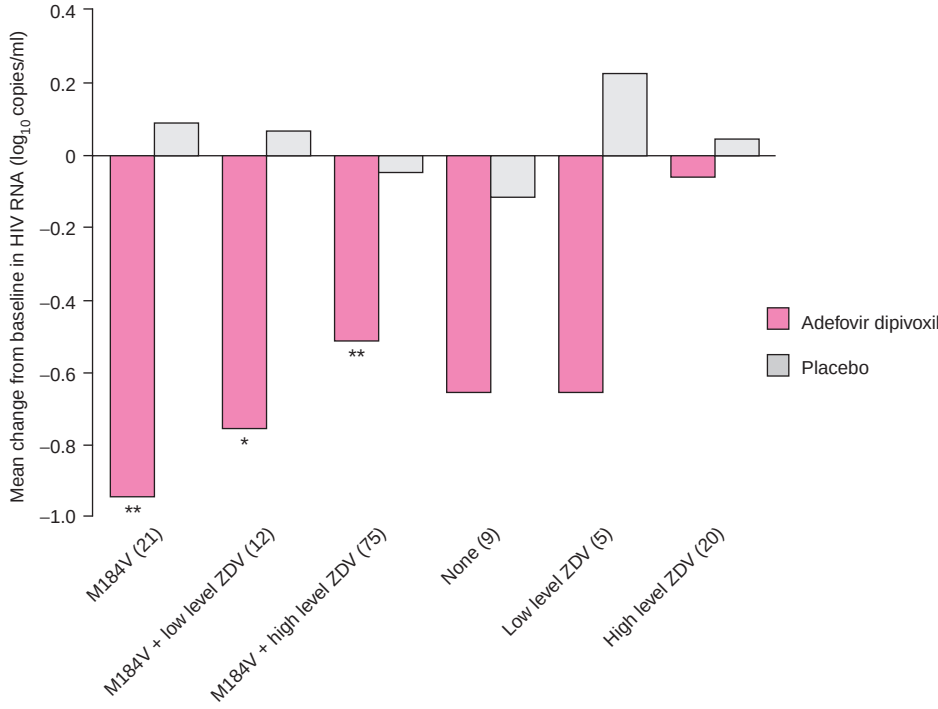


Fig. 2. Efficacy of adefovir dipivoxil against HIV isolates with lamivudine (M184V)- and/or zidovudine (ZDV)-associated mutations at baseline. Data from a prospective virological substudy (n = 142) of a randomised, double-blind multicentre trial comparing adefovir dipivoxil 120mg and placebo once daily in addition to standard antiretroviral therapy in 442 antiretroviral-experienced patients (study GS408; see text and figure 1 for more details).[38] Graph shows mean change from baseline in HIV RNA level after 24 weeks' treatment for patients grouped by viral mutations at baseline (number of patients). * p = 0.012, ** p ≤ 0.002 *vs* placebo.

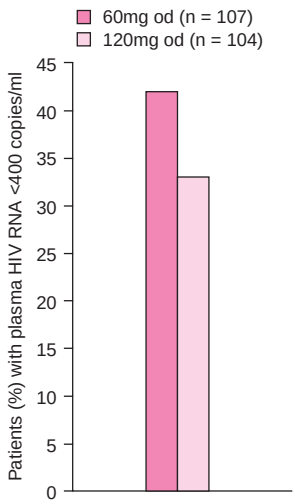


Fig. 3. Suppression of plasma HIV RNA with adefovir dipivoxil 60 and 120mg once daily (od) in addition to existing antiretroviral therapy in patients with HIV infection.[40] Incidence of patients with plasma HIV RNA below the level of detection (primary end-point) after 20 weeks in a randomised double-blind study in 211 patients with HIV RNA level ≥5000 copies/ml and CD4+ count ≥100 cells/μl.

Expanded Access Program had serious adverse events possibly or probably related to the drug, as defined by the investigator (nephrotoxicity, pancreatitis, fever, nausea with or without vomiting].[45] Patients received adefovir dipivoxil 60mg once daily, or 120mg once daily initially with subsequent reduction to 60mg after 16 weeks. Serious renal adverse events occurred in 3% of 1532 patients who received adefovir dipivoxil for ≥24 weeks.

- The incidence of grade 3 or 4 clinical adverse events did not differ significantly between patients receiving adefovir dipivoxil 120mg or placebo once daily (8 *vs* 5%) during the 24-week double-blind phase of the GS408 trial[38] (all patients also received standard antiretroviral therapy, see section 3 for more details of study design). In addition, the total incidence of grade 3 or 4 laboratory toxicity was similar in the 2 groups (33 *vs* 29%). Grade 3 or 4 ALT elevations were significantly more common with adefovir dipivoxil than with placebo (9 *vs* 4%), as was grade 3 or 4 hyperbilirubinaemia (6 *vs* 2%) [both p = 0.03 *vs* placebo].

- Renal data from 2 clinical trials indicate that nephrotoxicity associated with adefovir dipivoxil typically has a late onset (usually after 6 months' treatment).[38,40] Kaplan-Meier plots of data from the GS408 study indicate that ≈50% of patients receiving 120mg once daily will experience an increase in serum creatinine level of >0.5 mg/dl (>44 μmol/L) above baseline after 80 weeks of treatment. The incidence of grade 1, 2 and 3 elevated serum creatinine levels during up to 100 weeks' treatment was 23, 4 and 1%, respectively (no grade 4 events) [full methodology and number of evaluable patients not reported]. Incidences for hypophosphataemia were 14, 26, 18 and 4% for grades 1, 2, 3 and 4, respectively.[38]

- In the GS408 study, resolution of elevated serum creatinine levels [to <0.5 mg/dl (<44 μmol/L) above baseline] occurred within 20 weeks in 92% of affected patients (Kaplan-Meier estimate); all patients with hypophosphataemia had serum phosphate levels >2.0 mg/dl (>0.65 mmol/L)] within 20 weeks (Kaplan-Meier estimate).[38]

- Data from a randomised double-blind comparison of adefovir dipivoxil 60 and 120mg once daily suggest that nephrotoxicity is less frequent with the lower dosage regimen.[40] An analysis of the percentage of patients with hypophosphataemia [serum phosphate level <2.0 mg/dl (<0.65 mmol/L)] over 42 weeks' treatment indicated that the 60mg regimen was significantly less nephrotoxic (p = 0.003 *vs* 120mg). After 42 weeks, ≈27 *vs* ≈50% of patients had hypophosphataemia. A similar result was seen for patients with serum creatinine levels ≥0.5 mg/dl (≥44 μmol/L) above baseline (p = 0.05; ≈28 *vs* ≈40% at 42 weeks). The data cited above were estimated from a graph (107 patients randomised to 60mg, 104 to 120mg).

5. Adefovir Dipivoxil: Current Status

Adefovir dipivoxil is currently in late stage clinical development in patients with HIV infection. It has shown efficacy in reducing plasma HIV RNA

levels when used in addition to standard antiretroviral therapy; the main adverse events in clinical studies were GI disturbances, elevations in hepatic enzyme levels and renal abnormalities.

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