PRODUCT MONOGRAPH

PrAPO-ADEFOVIR

Adefovir Dipivoxil Tablets

10 mg

Antiviral Agent

APOTEX INC.
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Toronto, Ontario
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APO-ADEFOVIR
Adefovir Dipivoxil Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet / 10 mg	Lactose monohydrate, starch, croscarmellose sodium, magnesium stearate, talc

INDICATIONS AND CLINICAL USE

APO-ADEFOVIR (adefovir dipivoxil) is indicated for the treatment of chronic hepatitis B in adults with Compensated and decompensated liver disease with evidence of active viral replication, and either evidence of histologically active disease or elevation in serum aminotransferases (ALT or AST).

This indication is based on data from:

- two randomized, double-blind, placebo-controlled studies in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function evaluating histological response

- and a non-placebo controlled study in pre- and post-liver transplantation patients, with either compensated or decompensated liver function, and an active-controlled study in patients with lamivudine-resistant hepatitis B and compensated liver function, evaluating virological response. The clinical significance of a reduction in serum HBV DNA with respect to histological improvement could not be evaluated.

CONTRAINDICATIONS

APO-ADEFOVIR is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. **For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with adefovir dipivoxil. Hepatic function should be monitored closely in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted (see WARNINGS).**
- **Chronic administration of adefovir dipivoxil may result in nephrotoxicity. It is important to monitor renal function before and during treatment with adefovir dipivoxil (see WARNINGS). Patients at risk for or having underlying renal dysfunction and patients taking nephrotoxic agents are particularly at risk and should be monitored closely. Patients with renal insufficiency at baseline or during treatment may require dose adjustment (see DOSAGE AND ADMINISTRATION).**
- **HIV resistance may emerge in chronic hepatitis B patients with unrecognized or untreated human immunodeficiency virus (HIV) infection treated with anti-hepatitis B therapies, such as therapy with adefovir dipivoxil, that may have activity against HIV (see WARNINGS).**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals (see WARNINGS).**

General

APO-ADEFOVIR (adefovir dipivoxil) should not be administered concurrently with VIREAD® (tenofovir disoproxil fumarate) or tenofovir disoproxil fumarate-containing products including TRUVADA® (emtricitabine/tenofovir disoproxil fumarate combination tablet), ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate combination tablet), and COMPLERA™ (rilpivirine/emtricitabine/tenofovir disoproxil fumarate combination tablet).

Patients should be advised that therapy of chronic hepatitis B with adefovir dipivoxil has not been proven to reduce the risk of transmission of hepatitis B virus to others through sexual contact or blood contamination and therefore, appropriate precautions should still be taken.

Exacerbations of Hepatitis after Discontinuation of Treatment

Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with APO-ADEFOVIR. Patients who discontinue APO-ADEFOVIR should be monitored at repeated intervals for hepatic function. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

In clinical trials of adefovir dipivoxil, exacerbations of hepatitis (ALT elevations 10 times the upper limit of normal or greater) occurred in up to 25% of patients after discontinuation of adefovir dipivoxil. Most of these events occurred within 12 weeks of drug discontinuation. These exacerbations generally occurred in the absence of HBeAg seroconversion, and presented as serum ALT elevations in addition to re-emergence of viral replication. In the HBeAg-positive and HBeAg-negative studies in patients with compensated liver function, the exacerbations were not generally accompanied by hepatic decompensation. However, patients with advanced liver disease or cirrhosis may be at higher risk for hepatic decompensation. Although most events appear to have been self-limited or resolved with re-initiation of treatment, severe hepatitis exacerbations, including fatalities, have been reported. Therefore, patients should be closely monitored after stopping treatment.

Nephrotoxicity

Chronic administration of adefovir dipivoxil (10 mg once daily) may result in nephrotoxicity. Nephrotoxicity characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus was historically shown to be the treatment-limiting toxicity of adefovir dipivoxil therapy at substantially higher doses in HIV-infected patients (60 mg and 120 mg daily) and in chronic hepatitis B patients (30 mg daily). Patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents such as cyclosporine, tacrolimus, aminoglycosides, vancomycin and non-steroidal anti-inflammatory drugs are at risk for nephrotoxicity **(see ADVERSE REACTIONS)**. It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with adefovir dipivoxil.

It is important to monitor renal function in all patients before and during treatment with adefovir dipivoxil, particularly for those with pre-existing or other risks for renal impairment. There is limited safety and efficacy data in patients with renal impairment. Adefovir dipivoxil is not recommended for these patients unless the potential benefit outweighs the potential risk.
Patients with renal impairment at baseline or during treatment may require dose adjustment **(see DOSAGE AND ADMINISTRATION)**. The risks and benefits of adefovir dipivoxil treatment should be carefully evaluated prior to discontinuing adefovir dipivoxil in a patient with treatment emergent nephrotoxicity.

HIV Resistance

Prior to initiating adefovir dipivoxil therapy, HIV antibody testing should be offered to all patients. Treatment with anti-hepatitis B therapies, such as APO-ADEFOVIR, that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Adefovir dipivoxil has not been shown to suppress HIV RNA in patients, however, there are limited data on the use of adefovir dipivoxil to treat patients with chronic hepatitis B co-infected with HIV.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals.

A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with APO-ADEFOVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Duration of Treatment

The optimal duration of treatment with APO-ADEFOVIR has not been established. The relationship between treatment with APO-ADEFOVIR and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis is not known.

HBV Resistance

Long-term use of adefovir dipivoxil may result in emergence of HBV resistance. Resistance to adefovir dipivoxil can result in viral load rebound which may result in exacerbation of hepatitis B and, particularly in the setting of diminished hepatic function, lead to liver decompensation and possible fatal outcome. In order to reduce the risk of resistance, serum HBV virus level should be monitored during adefovir dipivoxil treatment and a change of treatment should be considered if serum HBV DNA remains above 1000 copies/mL after 48 weeks of treatment.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. APO-ADEFOVIR should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus **(see TOXICOLOGY, Pregnancy).** For patients who are on APO-ADEFOVIR and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of APO-ADEFOVIR.

Pregnancy Registry

To monitor fetal outcomes of pregnant women exposed to APO-ADEFOVIR, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-667-4708

Labor and Delivery

There are no studies in pregnant women and no data on the effect of adefovir dipivoxil on transmission of HBV from mother to infant. Therefore appropriate infant immunizations should be used to prevent neonatal acquisition of HBV.

Nursing Women

It is not known whether adefovir is excreted in human milk. Mothers should be instructed not to breastfeed if they are taking APO-ADEFOVIR.

Pediatrics

Safety and efficacy of APO-ADEFOVIR in pediatric patients have not been established.

Geriatrics

Clinical studies of adefovir dipivoxil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised when prescribing to elderly patients, since they have a greater frequency of decreased renal or cardiac function due to concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Experience in Patients with Compensated Liver Disease

Assessment of adverse reactions is based on two placebo-controlled studies (437 and 438) in which 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment with adefovir dipivoxil (N=294) or placebo (N=228) for 48 weeks. The most common treatment related adverse events in patients receiving adefovir dipivoxil were asthenia, headache, and abdominal pain.

In addition to specific adverse events described under the **WARNINGS AND PRECAUTIONS** section, all treatment-related clinical adverse events that occurred in 3% or greater of adefovir dipivoxil-treated patients compared with placebo are listed in Table 1. Patients who received adefovir dipivoxil up to 240 weeks in Study 438 reported adverse reactions similar in nature and severity to those reported in the first 48 weeks.

Table 1. Treatment-Related Adverse Events (Grades 1-4) Reported in ≥ 3% of ADV- Treated Patients in the Pooled 437-438 Studies (0-48 Weeks)

	Adefovir dipivoxil N=294	**Placebo N=228**
Body as a Whole		
Asthenia	13 %	14%
Headache	9%	10%
Abdominal pain	9%	11%
Digestive		
Nausea	5%	8%
Flatulence	4%	4%
Diarrhea	3%	4%
Dyspepsia	3%	2%

In addition, the following selected adverse events were reported in less than 3% of patients treated with adefovir dipivoxil:

BODY AS A WHOLE: back pain, chest pain

DIGESTIVE: anorexia

HEMATOLOGIC AND LYMPHATIC: anemia, thrombocytopenia

METABOLIC AND NUTRITIONAL: weight loss

RESPIRATORY: pharyngitis

SKIN AND APPENDAGES: rash

Laboratory Abnormalities

Laboratory abnormalities observed in these studies occurred with similar frequency in the adefovir dipivoxil and placebo treated groups with the exception of hepatic transaminase elevations which occurred more frequently in the placebo group. Increased liver transaminases were the most common post-treatment laboratory abnormality in the adefovir dipivoxil treated group **(see WARNINGS).** In addition, increased creatinine was identified as an adverse reaction with extended open-label treatment.

A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

Table 2. Grade 3-4 Laboratory Abnormalities Reported in ≥ 1% of All Adefovir Dipivoxil-Treated Patients in the Pooled 437-438 Studies (0-48 Weeks)

	Adefovir dipivoxil N=294	**Placebo N=228**
ALT (>5 x ULN)	20%	41%
Hematuria (≥ 3+)	11%	10%
AST (>5 x ULN)	8%	23%
CK (>4 x ULN)	7%	7%
Amylase (>2 x ULN)	4%	4%
Glycosuria ((≥ 3+)	1%	3%

No patients with adequate renal function treated with adefovir dipivoxil developed a serum creatinine increase ≥44 µmol/L (≥0.5 mg/dL) from baseline by Week 48. By Week 96, 10% and 2% of adefovir dipivoxil -treated patients, by Kaplan-Meier estimate, had increases in serum creatinine ≥ 27 µmol/L (≥0.3 mg/dL) and ≥44 µmol/L from baseline, respectively (no placebo-controlled results were available for comparison beyond Week 48). Of the 29 of 492 patients with elevations in serum creatinine ≥ 27 µmol/L from baseline, 20 out of 29 resolved on continued treatment (≤18 µmol/L or ≤0.2 mg/dL), 8 of 29 remained unchanged and 1 of 29 resolved on discontinuing treatment. Patients who received placebo during the first 48 weeks and adefovir dipivoxil during the second 48 weeks and patients who received adefovir dipivoxil during the first and second 48 weeks in Study 438 continued on adefovir dipivoxil for a median duration of 226 weeks (n=125); 4/125 patients (3%) had elevations in serum creatinine ≥44 µmol/L from baseline which resolved in 1 patient who permanently discontinued treatment and remained stable in 3 patients who continued treatment. In Study 437, 65 patients continued adefovir dipivoxil for a median duration of 234 weeks. Six patients had a confirmed increase of ≥ 44 µmol/L (≥ 0.5 mg/dL) from baseline with 2 patients discontinuing from the study due to the elevated serum creatinine concentration. **(See Laboratory Abnormalities – Special Risk Patients).**

Experience in Pre- and Post-liver Transplantation Patients with Lamivudine-Resistant HBV

Pre- (N = 226) and post-liver transplantation patients (N = 241) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with adefovir dipivoxil for up to 203 weeks, with a median time on treatment of 51 and 99 weeks, respectively**.**

The most common treatment-related adverse events reported in pre- and post-liver transplantation patients treated with adefovir dipivoxil with a 2% frequency or higher are shown in Table 3.

Table 3. Treatment-Related Adverse Events Reported in ≥2% of Pre- or Post-liver Transplantation Patients

	Pre-liver Transplantation N=226	Post-liver Transplantation N=241
Body as a Whole		
Asthenia	4%	6%
Abdominal pain	2%	5%
Headache	<1%	4%
Digestive		
Nausea	1%	5%
Vomitng	1%	3%
Diarrhea	2%	4%
Jaundice	<1%	2%
Metabolic and Nutritional		
ALT increase	1%	4%
AST increase	1%	3%
Hyperkalemia	0%	2%
Hypophosphaternia	2%	2%
Liver function tests abnormal	1%	2%
Musculoskeletal		
Myalgia	0%	3%
Skin and Appendages		
Pruritus	1%	5%
Rash	1%	2%
Urogenital		
Abnormal kidney function	1%	3%
Creatinine increase	2%	12%
Renal Failure	1%	2%

Fever. flatulence, hepatic failure, cough increase, pharyngitis and sinusitis occurred in less than 2 % of patients.

Laboratory Abnormalities – Special Risk Patients

Pre- (N = 226) and post-liver transplantation patients (N = 241) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with adefovir dipivoxil for up to 203 weeks, with a median time on treatment of 51 and 99 weeks, respectively. Changes in renal function occurred in pre- and and post-liver transplantation patients with risk factors for renal dysfunction, including concomitant use of cyclosporine and tacrolimus, renal insufficiency at baseline, hypertension, diabetes, and on-study transplantation. Increases in serum creatinine ≥44 µmol/L (≥0.5 mg/dL) from baseline were observed in 18%, 35%, and 35% of pre-liver transplantation patients by Weeks 48, 96, and 144, respectively, by Kaplan-Meier estimates. Increases in serum creatinine ≥44 µmol/L from baseline were observed in 12%, 28%, and 30% of post-liver transplantation patients by Weeks 48, 96, and 144, respectively, by Kaplan-Meier estimates. Elevations in serum creatinine ≥44 µmol/L from baseline resolved (≤27 µmol/L or ≤0.3 mg/dL increase from baseline) in 8 of 39 (21%) patients in the pre-liver transplantation cohort and in 14 of 43 (33%) patients in the post-liver transplantation cohort by the last study visit. Among patients who were assessed for serum

phosphorus, values <0.65 mmol/L were observed in 3/186 (1.6%) of pre-liver transplantation patients and in 6/208 (2.9%) of post-liver transplantation patients by last study visit. Four percent (19 of 467) of pre- and post-liver transplantation patients discontinued adefovir dipivoxil due to renal events.

Due to the presence of multiple concomitant risk factors for renal dysfunction in these patients, the contributory role of adefovir dipivoxil to these changes in serum creatinine and serum phosphorus is difficult to assess.

Post Market Adverse Drug Reactions

In addition to adverse reaction reports from clinical trials the following possible adverse reactions have also been identified during post-approval use of adefovir dipivoxil. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Metabolism and Nutrition Disorders: hypophosphatemia

Gastrointestinal Disorders: pancreatitis

Musculoskeletal System and Connective Tissue Disorders: Osteomalacia (manifested as bone pain and which may contribute to fractures) and myopathy, both associated with proximal renal tubulopathy.

Renal and Urinary Disorders: renal failure, Fanconi syndrome, proximal renal tubulopathy

DRUG INTERACTIONS

Since adefovir is eliminated by the kidney, coadministration of APO-ADEFOVIR (adefovir dipivoxil) with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or renally eliminated coadministered drugs.

At concentrations substantially higher (>4000 fold) than those observed in vivo, adefovir did not inhibit any of the following human CYP450 isoforms, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The potential for adefovir to induce CYP450 enzymes is unknown. Based on the results of these in vitro experiments and the known elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir with other medicinal products is low.

Adefovir dipivoxil has been evaluated in healthy volunteers in combination with lamivudine, trimethoprim/sulfamethoxazole, acetaminophen and ibuprofen and in post-liver transplantation patients in combination with tacrolimus.

The pharmacokinetics of lamivudine, trimethoprim/sulfamethoxazole, acetaminophen, tacrolimus, and ibuprofen were unaltered when coadministered with adefovir dipivoxil. The pharmacokinetics of adefovir were unaltered when adefovir dipivoxil was coadministered with lamivudine, acetaminophen, tacrolimus, and trimethoprim/ sulfamethoxazole. When adefovir dipivoxil was coadministered with ibuprofen (800 mg TID) increases in adefovir C_{max} (33%), AUC (23%) and urinary recovery were observed. This increase appears to be due to higher

relative oral bioavailability, not a reduction in renal clearance of adefovir. This increase was not considered to be of a sufficient magnitude to warrant a change in dosing of adefovir dipivoxil.

DOSAGE AND ADMINISTRATION

The recommended dose of APO-ADEFOVIR (adefovir dipivoxil) in chronic hepatitis B patients with adequate renal function is 10 mg, once daily, taken orally, without regard to food. The optimal duration of treatment is unknown **(see WARNINGS, Exacerbation of Hepatitis after Discontinuation of Treatment)**. Therapy should be initiated and monitored by a physician experienced in the management of chronic hepatitis B.

Discontinuation of APO-ADEFOVIR treatment and a change in treatment should be considered in case of evidence of ineffectiveness or efficacy loss.

Dosage Adjustment in Renal Impairment

Adefovir is eliminated by renal excretion, therefore adjustments in the dosing interval of APO-ADEFOVIR are required in patients with creatinine clearance < 50 mL/min.

The dosing frequency according to renal function must not exceed the recommended scheduled based on a pharmacokinetic study (see Table 4). Clinical response to treatment and renal function should be closely monitored in these patients.

Table 4. Dosing interval Adjustments of Adefovir Dipivoxil in Patients with Renal Impairment

	Creatinine Clearance (mL/min)*			
	≥50	**30-49**	**10-29**	**Hemodialysis Patients**
Recommended Dose and Dosing Interval	10 mg every 24 hours	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days following dialysis

*Creatinine clearance calculated by Cockcroft-Gault method using lean or ideal body weight.

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment **(see ACTIONS and CLINICAL PHARMACOLOGY, Special Populations and Conditions)**.

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The next dose should be taken at the regularly scheduled time the following day. The patient should not take two doses of APO-ADEFOVIR at once to make up for missing a dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

If overdose occurs, activated charcoal may be used to remove unabsorbed drug. The patient should be monitored for evidence of toxicity, and standard supportive treatment should be applied as necessary.

Following a single 10 mg dose of APO-ADEFOVIR (adefovir dipivoxil), a four-hour hemodialysis session removed approximately 35% of the adefovir dose.

Daily doses of adefovir dipivoxil 500 mg for 2 weeks and 250 mg for 12 weeks have been associated with gastrointestinal side effects (also, **see WARNINGS and PRECAUTIONS, NEPHROTOXICITY).**

ACTIONS AND CLINICAL PHARMACOLOGY

APO-ADEFOVIR is an oral prodrug of adefovir, a nucleoside phosphonate analog of adenosine monophosphate, which is actively transported into mammalian cells where it is converted into the active metabolite, adefovir diphosphate, by host enzymes. Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes. Adefovir diphosphate inhibits viral polymerases by direct binding competition with the natural substrate (deoxyadenosine triphosphate) and, after incorporation into viral DNA, results in DNA chain termination. The inhibition constant (Ki) for adefovir diphosphate for recombinant HBV DNA polymerase was 0.1µM. Adefovir diphosphate selectively inhibits HBV DNA polymerases at concentrations 12-, 700-, and 10-fold lower than those needed to inhibit human DNA polymerases α, β, and γ, respectively.

Adefovir has in vitro antiviral activity against hepadnaviruses. The in vitro IC_{50} (concentration of drug which inhibits viral replication by 50%) of adefovir against wild-type HBV varied from 0.2 µM – 1.2 µM in human hepatic cell lines (0.2 – 1.2 µM in HB611, and 0.7 – 1.2µM in HepG2 hepatoma cell lines).

Pharmacokinetics

The pharmacokinetics of adefovir have been evaluated in healthy volunteers and patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations. The pharmacokinetics of adefovir has also been investigated in patients with hepatic and renal impairment.

Absorption

Adefovir dipivoxil is a dipivaloyloxymethyl ester prodrug of the active ingredient adefovir.
The oral bioavailability of adefovir is approximately 59%.

Following oral administration of a single dose of APO-ADEFOVIR to chronic hepatitis B patients, the median (range) peak serum concentration (C_{max}) was achieved after 1.75 hrs (0.58 – 4.00). C_{max} and area under the curve (AUC) values were 16.70 (9.66 – 30.56) ng/mL and 204 (110 – 356) ng·h/mL, respectively. The median (range) oral clearance of adefovir was 304.90 (173.07 – 490.62) mL/hr/kg. Plasma adefovir concentrations declined in a biexponential manner with a median terminal elimination half-life of 7.22 hours (4.72 – 10.70 hours).

The pharmacokinetics of adefovir in subjects with adequate renal function were not affected following 10 mg once daily dose of APO-ADEFOVIR over 7 days. The effect of long term once daily administration of APO-ADEFOVIR on adefovir pharmacokinetics has not been studied.

Distribution

In vitro binding of adefovir to human plasma or human serum proteins is ≤ 4 % over the adefovir concentration range of 0.1 to 25 µg/mL. The volume of distribution at steady-state following intravenous administration of 1.0 or 3.0 mg/kg/day is 392 ± 75 and 352 ± 9 mL/kg, respectively.

Metabolism

Following oral administration, APO-ADEFOVIR is rapidly converted to adefovir. Forty-five percent of the dose is recovered as adefovir in the urine over 24 hours after multiple doses of APO-ADEFOVIR.

Excretion

Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion. The pharmacokinetics of APO-ADEFOVIR have been evaluated with a number of drugs that also undergo tubular secretion **(see DRUG INTERACTIONS).** Coadministration of APO-ADEFOVIR with other drugs that are eliminated by, or alter tubular secretion may increase serum concentrations of either adefovir or the administered drug.

Effects of Food on Oral Absorption

APO-ADEFOVIR may be taken without regard to food**.** Adefovir exposure was unaffected when APO-ADEFOVIR was administered with food (~1000 kcal high-fat meal).

Special Populations and Conditions

Pediatrics and Geriatrics

Pharmacokinetic studies have not been conducted in children or in the elderly.

Gender

The pharmacokinetics of adefovir were similar in male and female patients.

Race

No definitive studies have been performed. Results from two pharmacokinetic studies in healthy Chinese volunteers (N = 12 in single dose study and N = 20 in 7-day multiple dose study) reported similar pharmacokinetic results to historical data from various studies in healthy and chronic hepatitis B Caucasian volunteers and patients.

Renal Impairment

In subjects with moderately or severely impaired renal function or with end-stage renal disease (ESRD) requiring hemodialysis, C_{max}, AUC, and half-life (T1/2) were increased. It is recommended that the dosing interval of APO-ADEFOVIR is modified in these patients. **(see DOSAGE AND ADMINISTRATION)**.

In Table 5, the pharmacokinetics of adefovir in patients with varying degrees of renal impairment without chronic hepatitis B are described.

Table 5. Pharmacokinetic Parameters (Median) of Adefovir in Patients with Varying Degrees of Renal Function

Renal Function Group	Unimpaired N=7	Mild N=8	Moderate N=7	Severe N=10	ESRD N=8
Baseline creatinine clearance (mL/min)	> 80	50 – 80	30 – 49	< 30	NA*
C_{max} (ng/mL)	18.7	21.7	27.1	53.7	56.7
$AUC_{0-\infty}$ (ng·hr/mL)	200	281	466	1300	NA
CL/F (mL/min)	454	324	195	70	NA
CL_{renal} (mL/min)	211	149	86	35	NA

* NA = Not applicable

Hepatic Impairment

The pharmacokinetics of adefovir have been studied in patients with hepatic impairment without chronic hepatitis B. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in dosing is required in patients with hepatic impairment.

STORAGE AND STABILITY

APO-ADEFOVIR tablets should be stored in original container at controlled room temperature, 15-25°C (59-77°F) in a tightly closed container. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-ADEFOVIR 10 mg tablets: White to off-white, round, flat-faced bevelled edge tablet. Engraved “APO” on one side, “A10” on the other side. Bottles of 30 tablets.

Each APO-ADEFOVIR 10 mg tablet contains 10 mg of adefovir dipivoxil with the following non-medicinal ingredients: lactose monohydrate, starch, croscarmellose sodium, magnesium stearate, and talc.

PART II: SCIENTIFIC INFORMATION

Drug Substance

Common name: Adefovir dipivoxil

Chemical names: Di(pivaloyloxymethyl) [[2-(6-amino-9*H*purin-9-yl)ethoxy] methyl] phosphonate

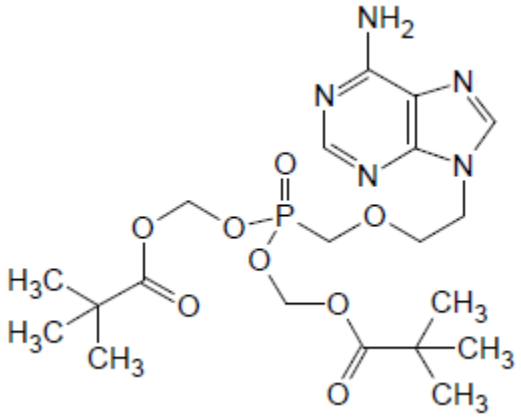
9-{2-[*O*,*O*'-Bis[(pivaloyloxy)methyl] phosphonomethoxy]ethyl}adenine

9-[2-[[Bis[(pivaloyloxy)methoxy]-phosphinyl]methoxy]ethyl]adenine

Molecular formula: $C_{20}H_{32}N_5O_8P$

Molecular weight: 501.47

Structural formula:



Physicochemical properties:

Physical description: White to off-white powder.

Solubility: Almost insoluble in *n*-hexane and diisopropyl ether. Soluble in dichloromethane acetone, ethanol, ethyl acetate, isopropanol.

Dissociation Constant: pK_a 4.16

pH: 4.98 (1% aqueous suspension)

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study was conducted under fasting conditions in twenty-six (26) healthy male volunteers. The rate and extent of absorption of adefovir was measured and compared following a single oral dose (1x 10 mg tablet) of Apo- Adefovir Dipivoxil Tablets and Hepsera® (Adefovir Dipivoxil) Tablets. The results from measured data are summarized in the following table:

Adefovir (1 x 10 mg) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng •h/mL)	258.3 261.2 (18.2)	261.1 263.5 (14.0)	98.9	95.5 − 102.5
AUC_{inf} (ng•h/mL)	274.0 277.3 (18.6)	277.3 280.0 (14.4)	98.8	95.3 − 102.4
Cmax (ng/mL)	23.5 23.7 (15.3)	23.8 24.2 (16.6)	98.8	93.6 − 104.2
T_{max}€ (h)	1.0 (0.3 – 2.5)	1.1 (0.3– 2.5)		
T_{half}§ (h)	8.8 (8.8)	9.0 (9.5)		

€ Expressed as the Median (range) only.
§ Expressed as the arithmetic mean (CV %) only.
* Apo-Adefovir (adefovir dipivoxil) 10 mg tablets, Apotex Inc.
† Hepsera® (adefovir dipivoxil) 10 mg Tablets are manufactured by Gilead Sciences Canada, Inc. and were purchased in Canada.

Study Demographics and Trial Design

HBeAg-Positive Chronic Hepatitis B

Study 437 was a randomized, double-blind, placebo-controlled, study in patients with HBeAg-positive chronic hepatitis B. Patients were serum HBsAg positive for a minimum of 6 months and HbeAg-positive at screening. At baseline, patients had a median total Knodell Histology Activity Index (HAI) score of 10 and a median serum HBV DNA level of 8.36 log10 copies/mL as measured by Roche Amplicor polymerase chain reaction (PCR) assay (LLOQ=1000 copies/mL), and a median ALT of 2.3 times the upper limit of normal. The median age of patients was 33 years, 74% were male, 59% were Asian, 36% were Caucasian, and 24% had prior interferon-α treatment, 2% had prior lamivudine treatment.

Presumed Precore Mutant (HBeAg-negative/anti-HBe-positive/ HBV DNA positive) Chronic Hepatitis B

Study 438 was a randomized (2:1), double-blind, placebo-controlled, two-arm study in patients with presumed precore mutant chronic hepatitis B. Patients were serum HBsAgpositive for a minimum of 6 months, HBeAg-negative at screening and anti-HBe-positive. At baseline, patients had a median total Knodell HAI score of 10, a median serum HBV DNA level of 7.08 log10 copies/mL as measured by the Roche Amplicor polymerase chain (PCR) reaction assay (LLOQ=1000 copies/mL), and a median ALT of 2.3 times the upper limit of normal. The median age of patients was 46 years, 83% were male, 66% were Caucasian and 30% were Asian, and 41% had prior interferon- α treatment, 8% had prior lamivudine, 8% had prior famciclovir.

Table 6. Studies 437 and 438 Trial Designs

Study No.	Trial Design	Dosage, Duration and Route of Administration	Study Subjects	Median Age	Gender
GS-98-437	Double-Blind Randomized Placebo-Controlled	Arm 1: 10 mg adefovir dipivoxil Arm 2: placebo 48 weeks duration	HBeAg-Positive Chronic Hepatitis. Arm 1 n =171 Arm 2 n = 167.	33 years	74% male
GS-98-438	Double-Blind Randomized Placebo-Controlled	<u>First 48 Weeks:</u> Arm 1: 10 mg adefovir dipivoxil Arm 2: placebo <u>Second 48 Weeks:</u> Arm 1 Re-randomized to adefovir dipivoxil or placebo (2:1 ratio) Arm 2 switched to adefovir dipivoxil 10 mg Weeks 49-96 All patients completing DB phase and on adefovir dipivoxil in year 2 were eligible for up to 144 week long term FU period	Presumed Pre-Core Mutant Patients. <u>First 48 weeks:</u> Arm 1 n=123 Arm 2 n=61. <u>Second 48 weeks:</u> Adefovir dipivoxil to placebo n=40. Adefovir dipivoxil to adefovir dipivoxil n=79. Placebo to adefovir dipivoxil n=60. Long term adefovir dipivoxil n=125	46 years	83% male

Study Results

The primary efficacy endpoint in both studies was histological improvement defined as ≥ 2 point decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score at Week 48; results of which are shown in Table 7. Post-baseline missing or unassessable biopsies were considered as treatment failures. Histological improvement was observed more frequently in patients treated with adefovir dipivoxil than in those treated with placebo after 48 weeks of treatment (see Table 7)**.** In Study 437, 53% of adefovir dipivoxil -treated patients had histological improvement compared to 25% of placebo-treated patients at Week 48. In Study 438, 64% of adefovir dipivoxil-treated patients had histological improvement compared to 33% of placebo-treated patients at Week 48.

Table 7. Histological Improvement at Week 48*

	Study 437		Study 438	
	Adefovir dipivoxil N = 168	**Placebo N = 161**	**Adefovir dipivoxil N = 121**	**Placebo N = 57**
Improvement**	53%	25%†	64%	33%††
No Improvement	36%	65%†	29%	63%††
Missing/ unassessable data***	11%	9%†	7%	4%††

† $p < 0.0001$ †† $p = 0.0002$

* Intent-to-treat population (patients with ≥ 1 dose of study drug) with assessable baseline biopsies.

** Histological improvement defined as ≥ 2 point decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score.

*** Post-baseline missing/unassessable biopsies were considered as treatment failures.

Table 8 illustrates the changes in Ishak Fibrosis Score by treatment group.

Table 8. Changes in Ishak Fibrosis Score at Week 48

Number of Adequate Biopsy Pairs*	Study 437		Study 438	
	Adefovir dipivoxil N = 150	**Placebo N = 146**	**Adefovir dipivoxil N = 112**	**Placebo N = 55**
Ishak Fibrosis Score Improved**	35%	19%	34%	15%
Unchanged	54%	59%	62%	49%
Worsened**	11%	22%	4%	36%

* Denominator is the number of patients with adequate biopsy at baseline and at Week 48, patients with missing biopsy information excluded.

** Change of 1 point or more in Ishak Fibrosis Score.

At Week 48, improvement was seen with respect to median change in serum HBV DNA (log10 copies/mL), normalization of ALT, and HBeAg loss and seroconversion as compared to placebo in patients receiving adefovir dipivoxil (Table 9).

Table 9. Change in Serum HBV DNA, ALT Normalization, HBeAg Loss and Seroconversion at Week 48

	Study 437		Study 438	
	Adefovir dipivoxil N = 171	**Placebo N = 146**	**Adefovir dipivoxil N = 150**	**Placebo N = 146**
Median change in serum HBV DNA from baseline (log10 copies/mL)	-3.52	-0.55	-3.91	-1.35
HBV DNA < 1000 copies/mL**	28%	0%	64%	3%
ALT normalization	48%	16%	72%	29%
HBeAg loss	24%	11%	NA*	NA*
HBeAg seroconversion	12%	6%	NA*	NA*

* Patients with HBeAg-negative disease cannot undergo HBeAg loss or seroconversion.
** Lower limit of quantification of the experimental Roche Amplicor™ polymerase chain reaction assay.

Genotypic and Phenotypic Analyses of Adefovir Dipivoxil

Resistance surveillance by genotypic analysis at baseline and Week 48 was performed in all adefovir dipivoxil treated patients with detectable serum HBV DNA (using the experimental Roche Amplicor PCR assay) in Study 437 (N = 215) and 438 (N = 56). During the study period, 48 weeks, no HBV DNA polymerase mutations were associated with decreased susceptibility to adefovir in cell culture and enzymatic assays (IC50 and Ki values were within 0.6- to 3.6- fold of wild-type) **(see MICROBIOLOGY for resistance surveillance beyond 48 weeks).**

Treatment Beyond 48 Weeks

In Study 438, patients who received adefovir dipivoxil during the first 48 weeks were re-randomized in a blinded manner to either continue on adefovir dipivoxil or receive placebo for an additional 48 weeks. Patients who continued on adefovir dipivoxil for an additional 48 weeks (N = 79) maintained suppression of serum HBV DNA levels (median HBV DNA change from baseline –3.47 log10 copies/mL; 71% < 1000 copies/mL) and have had sustained reductions in ALT levels (73% < ULN) similar to the results at 48 weeks (see Table 9)**.** In contrast, patients who discontinued adefovir dipivoxil (switched to placebo for additional 48 weeks; N = 40) had serum HBV DNA levels return towards baseline (median HBV DNA change from baseline –1.09 log10 copies/mL; 8% < 1000 copies/mL) and ALT levels rebounded (32% < ULN) in the majority of patients.

Patients who received placebo during the first 48 weeks and adefovir dipivoxil during the second 48 weeks and patients who received adefovir dipivoxil during the first and second 48 weeks continued on adefovir dipivoxil for up to 144 additional weeks for a total of up to 192 weeks of treatment (192-week cohort) or up to 240 weeks of treatment (240-week cohort), respectively. Following treatment with adefovir dipivoxil for 144, 192, and 240 weeks, 53 of 69 (77%), 51 of 65 (78%) and 37 of 55 (67%) patients in the 240-week cohort, respectively, had undetectable HBV DNA levels and 43 of 64 (67%), 44 of 59 (75%) and 38 of 55 (69%) patients had ALT normalization; similar percentages of undetectable DNA and ALT normalization were observed at Weeks 144 and 192 for patients who received adefovir dipivoxil in the 192-week cohort. Twelve of 22 (55%) patients treated with adefovir dipivoxil in the 192-week cohort and 17 of 24

(71%) patients treated in the 240-week cohort had an improved Ishak Fibrosis Score. In the combined 192-week and 240-week cohorts, 7 of 12 (58%) patients with bridging fibrosis or cirrhosis at baseline had an improved Ishak Fibrosis Score of ≥ 2 points after 192 weeks of treatment or 240 weeks of treatment with adefovir dipivoxil. In both cohorts, 6 of 125 patients (5%) who received adefovir dipivoxil experienced HBsAg loss. Five of these 6 patients also achieved and maintained HBsAg seroconversion (HBsAg-/HBsAb+).

Pre- and Post-Liver Transplantation Patients

Adefovir dipivoxil was also evaluated in an open-label, uncontrolled study of 467 chronic hepatitis B patients pre- (N = 226) and post- (N = 241) liver transplantation with clinical evidence of lamivudine-resistant HBV (Study 435). At baseline, 60% of pre-liver transplantation patients were classified as Child-Pugh-Turcotte score of Class B or C. The median baseline HBV DNA as measured by the Roche Amplicor polymerase chain reaction assay (LLOQ=1000 copies/mL) was 7.4 and 8.2 log10 copies/mL, and the median baseline ALT was 1.8 and 2.0 times the upper limit of normal in pre- and post-liver transplantation patients, respectively. Results of this study are displayed in Table 10. Treatment with adefovir dipivoxil resulted in a similar reduction in serum HBV DNA regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline.

Table 10. Efficacy in Pre- and Post – Liver Transplantation Patients at Week 48*

Efficacy Parameter	Pre-liver Transplantation N=(226)	Post-liver Transplantation (N=241)
Median change in HBV DNA from baseline (log10 copies/mL)	–4.1 (n=117)	–4.2 (n=164)
**Proportion with undetectable HBV DNA (< 1000 copies/mL)	71% (77 of 109)	40% (64 of 159)
Stable or improved Child-Pugh-Turcotte score	96%** (86 of 90)	93% (107 of 115)
Normalization of: *** ALT	74% (61 of 82)	51% (56 of 110)
Albumin	80% (43of 54)	81% (21 of 26)
Bilirubin	58% (38 of 66)	76% (29 of 38)
Prothrombin time	85% (39 of 46)	56% (5 of 9)

* Centrally assessed population defined as all patients with a baseline and at least one post-baseline HBV DNA result where the analysis was performed by the central laboratory.

** Denominator is the number of patients with serum HBV DNA ≥ 1000 copies/mL at baseline using the Roche Amplicor Monitor PCR Assay (LLOQ = 1000 copies/mL) and non-missing value at Week 48

*** Denominator is patients with abnormal values at baseline and non-missing values at Week 48.

Treatment Beyond 48 Weeks:

In the pre-liver transplantation cohort, 25 of 33 (76%) patients achieved undetectable HBV DNA levels (< 1000 copies/mL), and 16 of 19 (84%) patients had ALT normalization at

96 weeks. In the post-liver transplantation cohort, 61 of 94 (65%) and 35 of 45 (78%) of patients achieved undetectable HBV DNA levels (< 1000 copies/mL) and 46 of 66 (70%) and 15 of 26 (58%) patients had ALT normalization at 96 and 144 weeks, respectively.

Patients with Lamivudine Resistant HBV and Compensated Liver Disease

In Study 461, a double-blind, active-controlled study in 59 chronic hepatitis B patients with clinical evidence of lamivudine-resistant hepatitis B virus, patients were randomized to receive either adefovir dipivoxil monotherapy or adefovir dipivoxil in combination with lamivudine 100 mg or lamivudine alone. At Week 48, the median decrease in serum HBV DNA from baseline was 4.04 log10 copies/mL in the adefovir dipivoxil 10 mg arm and 3.59 log10 copies/mL in patients treated with adefovir dipivoxil in combination with lamivudine. The median decrease in serum HBV DNA from baseline in the lamivudine arm alone was 0. ALT normalized in 47% of patients treated with adefovir dipivoxil, in 53% of patients treated with adefovir dipivoxil in combination with lamivudine, and 5% of patients treated with lamivudine alone. The changes in serum HBV DNA over time are summarized in Table 11 below.

Table 11. Median Change in Serum HBV DNA –Study 461

	HBV DNA Median Change from Baseline (log10 copies/mL)		
	LAM N=19	ADV N=19	ADV + LAM N=20
Baseline Value	8.2	8.4	7.9
Change from Baseline to Week:			
4	0.1	-1.8	-1.9
8	0.0	-2.6	-2.5
12	-0.1	-2.6	-2.7
24	0.1	-3.4	-3.0
36	0.1	-3.8	-3.3
48	0.0	-4.0	-3.6

DETAILED PHARMACOLOGY

MICROBIOLOGY

In Vitro Cross-resistance

Preclinical studies: HBV engineered to encode DNA polymerase mutations, including YMDD mutations (rtL180M, rtM204I, rtM204V, rtL180M plus rtM204V plus rtV173L, rtL180M plus rtM204V,) remains susceptible to adefovir in cell-based assays of HBV replication. Mutations in the HBV DNA polymerase (rtT128N and rtR or rtW153Q) due to immune escape mutations in the overlapping gene for hepatitis B surface antigen, associated with resistance to hepatitis B immune globulin, do not affect susceptibility to adefovir in cell-culture assays of HBV replication. Adefovir also demonstrated in vitro activity against HBV variants with entecavir associated mutations (rtT184G, rtS202I, rtM250V).

HBV variants expressing the adefovir-associated resistance mutation rtN236T showed no change in susceptibility to entecavir in vitro and a 2- to 3-fold decrease in lamivudine susceptibility in vitro. The adefovir-associated resistance mutation rtA181V showed a range of decreased susceptibilities to lamivudine of 1- to 14-fold, and a 12-fold decrease in susceptibility to entecavir in vitro. In patients with either the rtA181V or the rtN236T mutation, a 2 to 6 log reduction in serum HBV DNA was observed when treatment with lamivudine was added to or substituted for treatment with adefovir dipivoxil.

Resistance

Clinical Studies

Monotherapy studies in nucleoside-naïve patients: In HBeAg-positive and HBeAg-negative patients in studies 437 and 438, respectively, no adefovir-associated resistance mutations were observed at Week 48. After median exposures of 135 weeks (range 88–179) and 189 weeks (range 110–235), the incidence of adefovir-associated resistance mutations (rtN236T or rtA181V/T) in HBeAg-positive patients (Study 437) was 3% and 17%, respectively. In HBeAg-negative patients (Study 438), the cumulative probability of adefovir-associated resistance mutations was 3%, 11%, 18 % and 29% at 96, 144, 192 and 244 weeks, respectively. Of the 29 HBe-Ag-negative patients who were treated for up to 240 weeks and developed adefovir-associated resistance mutations, 18 had a confirmed increase of ≥1 log10 HBV DNA copies/mL above nadir or never achieved HBV DNA levels below 4 log10 copies/mL while on treatment. In addition, the long term development of resistance to adefovir dipivoxil was significantly higher in patients with serum HBV DNA above 1000 copies/mL after 48 weeks of treatment.

Studies where adefovir dipivoxil was added to ongoing lamivudine in patients with lamivudine-resistance: In an open-label study of pre- and post-liver transplantation patients with clinical evidence of lamivudine-resistant hepatitis B virus (Study 435), the incidence of adefovir-associated resistance (rtN236T or rtA181V) mutations was 0% at 48 weeks. Four patients demonstrated the rtN236T mutation after 72 weeks of adefovir dipivoxil therapy. Development of the rtN236T mutation was associated with serum HBV DNA rebound. All 4patients who developed the rtN236T mutation in their HBV had discontinued lamivudine therapy before the development of genotypic resistance and all four lost the lamivudine associated mutations present at baseline. In a study of 35 HIV/HBV co-infected patients with lamivudine-resistant HBV (Study 460i) who added adefovir dipivoxil to lamivudine, no adefovir-associated mutations were observed up to144 weeks of therapy. **(See DESCRIPTION OF CLINICAL TRIALS).**

In Vitro Studies

Clinical isolates with genotypic changes conferring reduced in vitro susceptibility to nucleoside analog inhibitors for the treatment of HBV infection have been observed. Longterm resistance analyses performed by genotyping samples from all adefovir dipivoxiltreated patients with detectable serum HBV DNA determined that mutations rtN236T and rtA181V contribute to adefovir resistance. In vitro the rtN236T mutation conferred a 4- to 14-fold reduced susceptibility and the rtA181V mutation conferred a 2.5- to 4.2-fold reduced susceptibility to adefovir.

TOXICOLOGY

Renal tubular nephropathy characterized by histologic alterations and/or increases in BUN and serum creatinine was the primary dose-limiting toxicity associated with administration of adefovir dipivoxil in animals. Nephrotoxicity was observed in animals at systemic exposures

approximately 3 – 10 times higher than those in humans at the recommended therapeutic dose of 10 mg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice and rats receiving adefovir dipivoxil have been conducted. In mice, at doses of 1, 3, or 10 mg/kg/day, no treatment-related increases in tumor incidence were found at 10 mg/kg/day (systemic exposure was 10 times that achieved in human at a therapeutic dose of 10 mg/day). In rats dosed at 0.5, 1.5, or 5 mg/kg/day, no drug-related increase in tumor incidence was observed. The exposure at the high dose was four times that at the human therapeutic dose.

Adefovir dipivoxil was mutagenic in the in vitro mouse lymphoma cell assay (with or without metabolic activation), but was not clastogenic in the in vivo mouse micronucleus assay.

Adefovir was not mutagenic in microbial mutagenicity assays involving Salmonella typhimurium (Ames) and Escherichia coli in the presence and absence of metabolic activation. Adefovir induced chromosomal aberrations in the in vitro human peripheral blood lymphocyte assay without metabolic activation.

In reproduction toxicology studies, no evidence of impaired fertility was seen in male or female rats at doses up to 30 mg/kg/day.

Pregnancy

Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses up to 35 mg/kg/day, or in rabbits at 20 mg/kg/day. In a toxicokinetic study in pregnant animals, systemic exposure in rats given 25 mg/kg/day or rabbits given 20 mg/kg/day were approximately 23 and 40 times that in humans at the therapeutic dose.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (20 mg/kg/day, systemic exposure 38 times human), embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye bulge, umbilical hernia and kinked tail) were observed. No adverse effects on development were seen with adefovir administered intravenously to pregnant rats at 2.5 mg/kg/day (systemic exposure 12 times human).

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, adefovir dipivoxil should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Local Tolerance

Based on studies in laboratory animals, adefovir dipivoxil is a mild skin irritant, but is not an allergic skin sensitizer. Adefovir dipivoxil was a severe ocular irritant (without saline irrigation) in a primary eye irritation study in rabbits, but was a mild ocular irritant with saline irrigation. Therefore, following any ocular exposure, eyes should be rinsed as soon as possible to minimize irritation.

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PART III: CONSUMER INFORMATION

Pr **APO-ADEFOVIR**
Adefovir Dipivoxil Tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-ADEFOVIR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-ADEFOVIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- APO-ADEFOVIR is used to treat adults with continuing (chronic) infection with active hepatitis B virus

What it does:
- APO-ADEFOVIR binds to viral DNA to interfere with replication of the virus and helps lower the amount of hepatitis B virus in your body.
- APO-ADEFOVIR will not cure your chronic hepatitis B.
- APO-ADEFOVIR may help lower the amount of hepatitis B virus in your body.
- It is not known how long APO-ADEFOVIR may help your hepatitis.
- Sometimes viruses change in your body and medications no longer work. This is called drug resistance.
- It is not known if APO-ADEFOVIR will reduce your chances of getting liver cancer or liver damage (cirrhosis) from chronic hepatitis B.
- APO-ADEFOVIR does not stop you from spreading hepatitis B to others by sex or sharing needles. It is important to practice safe sex and not to share needles.

When it should not be used:
Together with your doctor, you need to decide whether APO-ADEFOVIR is right for you.
- Do not take APO-ADEFOVIR if you are allergic to any of the ingredients in APO-ADEFOVIR **(see What the nonmedicinal ingredients are)**.
- Do not take APO-ADEFOVIR if you are HIV positive.
- Do not take APO-ADEFOVIR if you are pregnant or breastfeeding.
- APO-ADEFOVIR has not been studied in adults over the age of 65 or in persons under 18 years of age.
- Do not take APO-ADEFOVIR if you are also taking VIREAD® (tenofovir disoproxil fumarate), TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), ATRIPLA® (efavirenz/emtricitabine/ tenofovir disoproxil fumarate), or COMPLERA™ (rilpivirine/ emtricitabine/tenofovir disoproxil fumarate).

What the medicinal ingredient is:
Adefovir dipivoxil

What the non-medicinal ingredients are:
Lactose monohydrate, starch, croscarmellose sodium, magnesium stearate, talc

What dosage forms it comes in:
10 mg tablets

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Talk to your doctor before you stop taking APO-ADEFOVIR.** Some people who take APO-ADEFOVIR get a very serious hepatitis when they stop taking APO-ADEFOVIR. This usually happens within 12 weeks after you stop APO-ADEFOVIR. You will need to have regular blood tests to check for liver function and hepatitis B virus levels if you stop taking APO-ADEFOVIR.
- **APO-ADEFOVIR may cause kidney problems**. This can happen to anyone that uses APO-ADEFOVIR, especially people who already have kidney problems. Your doctor may ask you to have blood tests to check for kidney function while you are taking APO-ADEFOVIR. Since kidney problems often do not cause symptoms and are often only detected with blood tests, it is important to have all of your blood tests as instructed by your doctor.
- **If you get or have HIV infection (the virus that causes AIDS)**, and you don't know it, or if your HIV is not being treated while you are taking APO-ADEFOVIR, APO-ADEFOVIR may increase the chances of you developing resistance to HIV infection, as APO-ADEFOVIR may have some anti-HIV activity. You should talk to your doctor to find out if you should have an HIV test before you start taking APO-ADEFOVIR and whenever there is a chance that you were exposed to HIV.
- **Some people who have taken nucleotide analog medications like APO-ADEFOVIR, either alone or in combination with other anti-retroviral drugs, have developed a serious condition called lactic acidosis (buildup of acid in the blood).** Lactic acidosis is a medical emergency and must be treated in the hospital. **(See Serious Side Effects, How Often They Happen and What To Do About Them section for symptoms). Some people who have taken medications like APO-ADEFOVIR, have developed serious liver problems** called hepatoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **(See Serious Side Effects, How Often They Happen and What To Do About Them section for symptoms).** You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleotide analog medicines, like APO-ADEFOVIR, for a long time.

Before starting APO-ADEFOVIR and to get the best possible treatment, be sure to tell your doctor if you:

- You know that you are pregnant or suspect that you may be pregnant, so that you can discuss the risk and benefit of taking APO-ADEFOVIR. It is not known if APO-ADEFOVIR can harm your unborn child.
- You are breastfeeding.
- You have kidney problems now or had them before.
- You are taking other medications that affect how your kidneys work.
- You think you may have HIV (the virus that causes AIDS).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medications you take. Some medications may affect how APO-ADEFOVIR (adefovir dipivoxil) works, especially medications that affect how your kidneys work. Do not take any other medications while you are taking APO-ADEFOVIR, until you have checked with your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:

- The usual adult dose is one APO-ADEFOVIR 10 mg tablet orally (by mouth) once a day.
- Your doctor may prescribe a different dosing schedule if you have problems with your kidneys.
- APO-ADEFOVIR may be taken with or without food.
- Do not stop taking APO-ADEFOVIR without consulting your doctor.

Overdose:

For management of a suspected drug overdose, or in case of an actual overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss your regular time for taking your dose, but then remember it during that same day, take your missed dose immediately.
- Then, take your next dose at the regularly scheduled time the following day.
- Do not take two doses of APO-ADEFOVIR at once to make up for missing a dose.
- If you are not sure what to do if you miss taking your medication check with your doctor or pharmacist for further instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of APO-ADEFOVIR are: weakness, headache, stomach pain, nausea, diarrhea, flatulence (intestinal gas) and indigestion.

The most common side effects of APO-ADEFOVIR in patients with chronic hepatitis B having a liver transplant are: weakness, stomach pain, headache, nausea, vomiting, diarrhea, rash and itching. Some patients also had undesirable effects on their kidneys, including kidney failure and damage to kidney cells.

Other possible side effects may include: muscle pain, muscle weakness, bone pain and softening of the bone (which may contribute to fractures) which are associated with kidney problems, and inflammation of the pancreas.

These are not all the possible side effects of APO-ADEFOVIR. Your doctor, nurse or pharmacist can discuss with you a more complete list of possible side effects with APO-ADEFOVIR. You should report any new or continuing symptoms to your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Stop taking drug and seek immediate and emergency medical attention
Rare (approximately 1 in 1,000 patients)	**Symptoms:**	
	You feel very weak or tired.	✳
	You have unusual (not normal) muscle pain.	✳
	You have stomach pain with nausea and vomiting.	✳
	You feel cold especially in your arms and legs.	✳
	You feel dizzy or lightheaded.	✳
	You have fast or irregular heartbeat.	✳
	Effect: Lactose acidosis	
Very Rare (approximately 1 in 10,000 patients)	**Symptoms:**	
	Your skin or the white part of your eyes turns yellow (jaundice).	✳
	Your urine turns dark.	✳
	Your bowel movements (stools) turn light in color.	✳
	You don't feel like eating food for several days or longer.	✳
	You feel sick to your stomach (nausea).	✳
	You have lower stomach pain.	✳
	Effect: Severe liver problems called hepatotoxicity with liver enlargement (hepatomegaly) and fat in the liver (steatosis)	

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleotide analog medicines, like APO-ADEFOVIR, for a long time.

This is not a complete list of side effects. For any unexpected effects while taking APO-ADEFOVIR, contact your doctor or pharmacist.

HOW TO STORE IT

APO-ADEFOVIR tablets should be stored in original container at controlled room temperature, 15-25°C (59-77°F) in a tightly closed container. Protect from moisture.

IMPORTANT: PLEASE READ

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:
1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products.

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