

Hepatitis B Agents Review

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Hepatitis B Agents Review

FDA-Approved Indications

Drug	Manufacturer	Indication
adefovir dipivoxil (Hepsera [®]) ¹	Gilead Sciences	Chronic hepatitis B virus (HBV) infection in patients ≥ 12 years of age with active viral replication with evidence of persistent elevation of alanine aminotransferase (ALT) or histologically active disease
entecavir (Baraclude [™]) ²	Bristol Myers Squibb	Chronic HBV infection in adults with evidence of active viral replication and either persistent elevations of serum aminotransferases (ALT or aspartate aminotransferase [AST]) or histologically active disease
lamivudine (EpiVir HBV [®]) ³	GlaxoSmithKline	Chronic HBV infection in adults and children two years and older with active viral replication
telbivudine (Tyzeka [®]) ⁴	Novartis	Chronic HBV infection in adults with evidence of active viral replication and either persistent elevations of ALT or AST or histologically active disease

Subpopulations whose treatment of chronic HBV infection is FDA-Approved^{5,6,7,8}

Study population	adefovir (Hepsera)	entecavir (Baraclude)	lamivudine (EpiVir HBV)	telbivudine (Tyzeka)
hepatitis B e Antigen (HBeAg)-positive or HBeAg-negative	X Compensated liver disease	X Compensated liver disease	X Compensated liver disease	X Compensated liver disease
lamivudine resistance mutations	X Compensated and decompensated liver disease	X Compensated liver disease	--	--
telbivudine resistance mutations	--	X	--	--
HIV/HBV co-infection	--	X With prior treatment with lamivudine	X Use HIV dose of 150 mg twice daily	--
Children	X 12-18 yrs	X ≥ 16 yrs	X > 2-17 yrs	--

Tenofovir disoproxil fumarate (Viread[®]) by Gilead Sciences is indicated for the treatment of chronic HBV infection in adults and as combination therapy with other antiretroviral agents for the treatment of HIV-1 infection in adults.⁹ The use of tenofovir in chronic HBV infection is based on data from one year of treatment in primarily nucleoside treatment-naïve adults with HBeAg-positive and HBeAg-negative chronic HBV infection with compensated liver disease. The numbers of patients in clinical trials who were nucleoside-experienced or had lamivudine-associated mutations at baseline were too small to impact conclusions of efficacy. Tenofovir has not been evaluated in patients with decompensated liver disease. Tenofovir is given as 300 mg orally daily without regard to food.

Peginterferon alfa-2a (Pegasys[®]) by Roche is indicated for the treatment of adult patients with HBeAg-positive or HBeAg-negative chronic HBV who have compensated liver disease and evidence of viral replication and liver inflammation.¹⁰ Peginterferon alfa-2a is self-administered as a subcutaneous injection once weekly for 48 weeks.

Recombinant interferon alfa-2b (Intron[®] A) by Schering-Plough is indicated for the treatment of chronic hepatitis B in patients one year of age or older with compensated liver disease. Patients who have been serum HBsAg-positive for at least six months and have evidence of HBV replication with elevated serum ALT are candidates for treatment. Interferon alfa-2b is given as a daily or three times weekly injection.

Overview

Chronic hepatitis B virus (HBV) affects an estimated 800,000 to 1.4 million persons in the United States and approximately 350 million persons worldwide.¹¹ In 2007, the number of acute HBV cases in the United States reported to the Centers for Disease Control and Prevention (CDC) dropped to 4,519. However, many HBV infections are asymptomatic or are never reported; the actual number of new HBV infections is estimated to be ten-fold higher.¹² Some communities are finding newly diagnosed HBV infections are most often found in adult immigrants to the US.¹³ Outside the US, many chronic infections result from vertical transmission, with a high prevalence of chronic infections in Asia.¹⁴

Chronic HBV infection is defined as persistence of hepatitis B surface antigen (HBsAg) for more than six months, high levels of HBV DNA, and presence of hepatitis B e Antigen (HBeAg) in the serum.¹⁵ Chronic HBV infection occurs in approximately five to ten percent of individuals with acute HBV infection. Long-term effects of chronic HBV infection include cirrhosis, liver failure, and hepatocellular carcinoma. HBV infections acquired by infants or children are significantly more likely (90 percent) to progress to chronic HBV infections as compared to adults (less than five percent).^{16,17}

The CDC has recommended testing for HBV in the following patient groups: pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected persons, persons born in countries with HBsAg prevalence of \geq eight percent, persons who are the source of blood or body fluid exposures that might warrant post-exposure prophylaxis (e.g., needle stick injury to a health care worker or sexual assault), and persons infected with HIV.¹⁸ In September 2008, the CDC recommended routine testing for HBsAg for additional populations with HBsAg prevalence of \geq two percent: persons born in geographic regions with HBsAg prevalence of \geq two percent, men who have sex with men, and injection-drug users.

The ultimate goal is to eliminate HBV transmission in the United States by broadening recommendations for HBV immunization. The HBV vaccine series is now offered to infants and

children in the United States to reduce the risk of chronic HBV infection. The estimated number of new acute HBV infections in the United States has significantly declined from 260,000 infections yearly in the 1980's to approximately 43,000 infections in 2007 with the greatest reduction seen among infants and children.¹⁹ The 2009 report by the Advisory Committee on Immunization Practices (ACIP) recommends universal vaccination of all infants beginning at birth and vaccine administration to unvaccinated children and adolescents.²⁰ In facilities treating adults at risk for HBV, such as sexually transmitted disease/HIV testing and treatment facilities, drug abuse treatment and prevention settings, health-care settings that target services to intravenous drug users or men who have sex with men, and correctional facilities, ACIP recommends universal HBV vaccination for all unvaccinated adults.²¹ In other medical settings where adults at risk for HBV infection receive care, health-care providers should inform all patients about the health benefits of vaccination, including risks for HBV infection and persons for whom vaccination is recommended, and vaccinate adults who report risks for HBV infection and any adults requesting protection from HBV infection.

In chronic HBV infection, viral replication is most active in the initial years of the infection and is characterized by the presence of HBeAg and HBV DNA in the serum. Active replication causes necrosis and inflammation of the liver identified as an elevation in alanine aminotransferase (ALT) levels. Often, with increased duration of infection, viral replication decreases with a loss of HBeAg and HBV DNA from the serum that occurs at a rate of five to 15 percent annually. Reactivation can occur and has been reported in patients receiving chemotherapy for unrelated cancer diagnoses.

In some patients, HBeAg is cleared from the serum due to a genetic mutation in the HBV DNA genome, but HBV DNA remains present.²² While the HBV DNA levels are typically lower in HBeAg-negative disease, seroconversion from HBeAg to anti-HBeAg cannot be used as an endpoint for therapy. HBeAg-negative patients tend to have relapse following discontinuation of antiviral therapy; therefore, duration of therapy is considered indefinite.

Decision to initiate treatment is determined by the risk/benefit ratio and considering the following factors: patient's age, severity of liver disease based on liver biopsy, ALT levels, HBV DNA levels, likelihood of response, HBeAg status (positive or negative), potential adverse effects, and possible complications.^{23,24}

In 2008, a treatment algorithm for the management of HBV was updated based on a review of evidence identified in a systematic review.²⁵ Highlights of the algorithm include the treatment goal of antiviral therapy is durable suppression of serum HBV DNA to low or undetectable levels. Baseline levels of HBV DNA and monitoring of antiviral therapy response should be performed using assays which can detect HBV DNA as low as 10 units/mL. Interferon alfa-2b (Intron A), lamivudine (Epivir HBV), adefovir (Hepsera), entecavir (Baraclude), peginterferon alfa-2a (Pegasys), telbivudine (Tyzeka), and tenofovir (Viread) are approved as initial therapy for chronic hepatitis B and have certain advantages and disadvantages. The 2008 treatment algorithm states that entecavir, tenofovir, and telbivudine are the most potent oral agents and have shown superiority to comparable agents in randomized clinical trials. The long-term use of lamivudine is limited by the development of resistance; however, lamivudine is well-tolerated with a good safety profile and efficacy. Lamivudine is not recommended for first-line use except in special circumstances such as patients receiving short-term antiviral prophylaxis during chemotherapy or pregnancy, as part of an HIV regimen in patients with HIV-HBV coinfection, or in combination with adefovir or tenofovir in patients with hepatic decompensation. Patients who require more than one year of treatment are best treated with entecavir or tenofovir due to the lower rates of viral resistance. First-line therapies according to 2008 treatment algorithm are

entecavir, peginterferon alfa-2a, or tenofovir due to the superior potency and low rates of viral resistance. Issues for consideration for therapy include efficacy, safety, rate of resistance, method of administration, and cost. Combination therapy is not universally recommended for all patients undergoing treatment for chronic HBV. Combination therapy may be considered a treatment option in those patients who are least able to afford the emergence of resistance including patients with cirrhosis, patients with anti-HBV drug resistance or history of suboptimal response, or in the setting of treatment of HIV-HBV coinfection.

Treatment guidelines from the American Association for the Study of Liver Diseases (AASLD) on chronic HBV infection were updated in September 2009. Considerations for treatment include safety and efficacy of the treatment, risk of drug resistance, cost of medication and monitoring, comorbidities and other viral infections, as well as patient and prescriber preference.²⁶ Due to the high rate of drug resistance during long term treatment, lamivudine and telbivudine are not preferred treatments for chronic hepatitis B except when only a short course of treatment is planned. Adefovir is less potent than the other oral antivirals, and it is associated with increasing viral resistance rates after the first year of therapy. Adefovir is a second-line agent for treatment-naïve patients. The first-line drugs for the treatment of chronic hepatitis B according to the AASLD are peginterferon alfa-2a, entecavir, and tenofovir.

Interferon alfa-2b and pegylated interferon alfa-2a, both injectable medications, are indicated for the treatment of chronic HBV infection but are not reviewed here. The interferons are generally used as monotherapy. Studies of the combination of pegylated interferons and lamivudine do not demonstrate consistent benefit from combination therapy compared to pegylated interferon monotherapy.^{27,28,29,30,31,32} The addition of lamivudine to interferon alfa-2b provides no significant clinical benefit.³³ Interferons have the advantage of avoiding the issue of viral resistance; however, the safety and tolerability profile may limit the use of the interferons.

Goal of antiviral therapy for chronic HBV infection is to eliminate or suppress the replication of HBV and to decrease the risk of progression to cirrhosis, hepatocellular carcinoma, or liver failure, which may eventually lead to death or liver transplantation.^{34,35} Treatment responses are evaluated on the basis of biochemical (normalization of serum ALT level), virologic (sustained clearance of HBeAg and HBV DNA), and histologic (decrease in inflammation on liver biopsy) parameters. Seroconversion is defined as the loss of HBeAg, undetectable HBV DNA, and the presence of an antibody to HBeAg. Antivirals for HBV infection should suppress HBV viral replication to the lowest level possible with other goals of treatment being histological improvement and ALT normalization. In 2008, Agency for Healthcare Research and Quality (AHRQ) issued an Evidence Report on the treatment of chronic Hepatitis B. Based on the available information, there was insufficient evidence to determine if biochemical, viral, or histological measures are valid surrogates of treatment effect on mortality, liver failure, or cancer. Monotherapy or combined drug therapy improves selected virological, biochemical, and histological markers with no consistent effects on all examined outcomes. The report stated that long term data and effect on all-cause mortality are needed.

This review will focus on adefovir dipivoxil, entecavir, lamivudine, and telbivudine.

Pharmacology

Adefovir dipivoxil (Hepsera) is an acyclic nucleotide analog of adenosine monophosphate. Adefovir is phosphorylated to active adefovir diphosphate. Adefovir diphosphate inhibits HBV DNA polymerase by competing with the natural substrate and causing DNA chain termination once it is incorporated in viral DNA.³⁶

Entecavir (Baraclude) is a guanosine nucleoside analog, phosphorylated *in vivo* to the triple phosphate active form. Entecavir triphosphate then inhibits three functions of viral HBV polymerase enzyme: base priming, reverse transcription from viral RNA, and HBV DNA synthesis.

Lamivudine (EpiVir HBV) is a synthetic nucleoside analog that is phosphorylated and incorporated in the viral DNA by the HBV polymerase; termination of the DNA chain results. Lamivudine is the (-) enantiomer of the dideoxy analog of cytidine.^{37,38}

Telbivudine (Tyzeka) is a synthetic nucleoside analog that also works by inhibiting HBV DNA polymerase.³⁹ Telbivudine undergoes phosphorylation to the triple phosphate active form and competes with thymidine for incorporation into HBV DNA. Telbivudine causes HBV DNA chain termination.

Viral Drug Resistance

Prolonged antiviral therapy is required for the suppression of chronic HBV infection. Antiviral resistance is initially manifested as breakthrough virologic infection. In most patients, this is followed by biochemical breakthrough and, in some patients, hepatitis flares and hepatic decompensation. Rapid and sustained suppression of viral replication is the best method to reduce the risk of viral resistance development.⁴⁰ For successful therapy, antivirals should be potent with a low rate of genotypic resistance, and patient compliance should be reinforced. If resistance is identified, the addition of another drug without an overlapping resistance profile should be given as early as possible, preferably at the time when genotypic resistance emerges.

Viral resistance is present in 15 to 30 percent of patients after twelve months of lamivudine therapy in both adult and pediatric patients.^{41,42,43} After three years of lamivudine therapy, the rate of lamivudine resistance is over 50 percent.⁴⁴ The most frequently studied mutation conferring lamivudine resistance is the YMDD-variant consisting of point mutations in the HBV polymerase gene.⁴⁵ Reduced clinical response is associated with lamivudine resistance. Once antiviral-resistant HBV mutants have been selected, the mutants are retained in the virus population even if the treatment is stopped. Lamivudine-resistant HBV strains have been detected up to four years after withdrawal of lamivudine.⁴⁶

Entecavir shows some cross-resistance with lamivudine and telbivudine; however, larger doses of entecavir can overcome some degree of reduced lamivudine susceptibility.⁴⁷ Entecavir-resistant HBV strains are susceptible to adefovir in an *in vitro* cell culture.⁴⁸ In one study with nucleoside analog treatment-naïve patients, entecavir resistance is rare; HBV DNA levels were suppressed to undetectable levels in 91 percent of enrolled patients.⁴⁹

While several trials lasting up to 72 weeks have not identified adefovir resistance, it has been reported.^{50,51,52,53,54,55} HBV resistance to adefovir has been observed in patients receiving adefovir for up to 252 weeks. Virologic failure has been observed in those patients with adefovir-resistant HBV strains.⁵⁶ In some HBV strains with mutations creating a reduced susceptibility to adefovir, a reduction in susceptibility to lamivudine was also noted.⁵⁷ Adefovir-resistant HBV strains remain susceptible to entecavir.⁵⁸

HBV resistance due to mutations in amino acids has been detected after 52 weeks of telbivudine in patients with $\geq 1,000$ copies/mL of HBV DNA.⁵⁹ Telbivudine selects for mutations in the YMDD motif like lamivudine. Some lamivudine-resistant strains of HBV have reduced susceptibility or are resistant to telbivudine.⁶⁰ One strain of adefovir-resistant HBV identified by the mutation in amino acid remained susceptible to telbivudine.

According to the 2008 treatment algorithm and the 2009 AASLD guidelines for chronic HBV, telbivudine is associated with a moderate rate of resistance.^{61,62} Low rates of resistance and sustained suppression can be achieved with telbivudine if HBV DNA levels are undetectable by week 24 in patients who are HBeAg-positive. Neither the 2008 algorithm nor the 2009 AASLD guidelines list telbivudine as a preferred agent because the rate of resistance to telbivudine is higher than rates of resistance observed with entecavir and tenofovir. Long-term surveillance of resistance rates with telbivudine has not been performed.

Cross-resistance has been observed among HBV reverse transcriptase inhibitors. *In vitro* assays of HBV strains with multiple substitutions with resistance to lamivudine and telbivudine showed reduced susceptibility to tenofovir.⁶³ HBV strains with resistance to entecavir also showed reduced susceptibility to tenofovir. HBV strains with adefovir-associated resistance substitutions showed reductions in susceptibility to tenofovir ranging from 2.9 to 10-fold that of wild type virus.

Telbivudine does not negatively impact the effect of HIV-specific therapies including abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine.⁶⁴

Entecavir does have the potential to cause development of viral resistance to HIV nucleoside reverse transcriptase inhibitors if used to treat chronic HBV infection in patients with HIV infection who are not being treated with highly active antiretroviral therapy (HAART).⁶⁵

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion
adefovir dipivoxil (Hepsera) ⁶⁶	59	7.5	none	Predominantly renal
entecavir (Baraclude) ⁶⁷	--	128-149	two minor: glucuronide and sulfate conjugates	Predominantly renal
lamivudine (Epivir HBV) ⁶⁸	86	5-7	minor: trans-sulfoxide	Predominantly renal
telbivudine (Tyzeka) ⁶⁹	--	~15	none	Predominantly renal

Contraindications/Warnings^{70,71,72,73}

All agents are contraindicated in patients who have previously demonstrated hypersensitivity to the individual drug or its components.

All of these agents have boxed warnings regarding the risk of severe acute exacerbation of hepatitis B following discontinuation of therapy. Approximately 25 percent of patients will have an increase in liver enzymes within the first 12 weeks after stopping therapy.

A black box warning for this category states lactic acidosis and severe hepatomegaly with steatosis have been rarely reported for all agents in this category.

adefovir (Hepsera)

An additional black box warning appears in the labeling for adefovir. Patients with or at risk for renal dysfunction require close monitoring during chronic adefovir therapy due to the risk of nephrotoxicity. Monitor renal function closely in these patients. Creatinine clearance should be calculated for all patients prior to initiating therapy. Dose adjustment of adefovir is necessary in adult patients with renal impairment (see Dosages chart). No dosing adjustment data are available for pediatric patients with renal impairment.

An early trial evaluated the potential for nephrotoxicity with adefovir.⁷⁴ Nephrotoxicity was observed in trials in patients with HIV at doses of 60 to 120 mg daily, which is far higher than the recommended daily dose of adefovir for HBV of 10 mg. In two double-blind, placebo-controlled trials, patients with chronic HBV and compensated liver disease with evidence of HBV replication were given adefovir 10 or 30 mg daily. Renal analysis found no significant change in serum creatinine or serum phosphorus levels after 48 weeks of therapy in the adefovir 10 mg daily group. A small increase of 0.2 mg/dL of median serum creatinine levels was observed. A decrease of 0.1 mg/dL of serum phosphorus at week 48 in the adefovir 30 mg daily group was observed. No patients met the nephrotoxicity criteria defined as an increase of ≥ 0.5 mg/dL from baseline for serum creatinine or a serum phosphorus value of less than 1.5 mg/dL on two consecutive occasions in the adefovir 10 mg group of a median of 48 weeks of observation.

HIV resistance in unrecognized or untreated patients with HIV may emerge with chronic HBV therapy with adefovir. Testing for HIV co-infection prior to treatment for HBV is recommended.

For patients with lamivudine-resistant HBV, use adefovir dipivoxil in combination with lamivudine. For all patients, consider modifying treatment when serum HBV DNA level remains above 1,000 copies/mL with continued treatment.

Adefovir dipivoxil should not be used concurrently with tenofovir (Viread) or tenofovir-containing products such as emtricitabine/tenofovir disoproxil fumarate combination tablet (Truvada[®]) and efavirenz/emtricitabine/tenofovir disoproxil fumarate combination tablet (Atripla[®]).

entecavir (Baraclude)

In 2007, an additional black box warning was added to the labeling for entecavir. Based on limited clinical experience, potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors exists if entecavir is used to treat chronic HBV infection in patients not receiving treatment for HIV co-infection. Entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving HAART.

lamivudine (EpiVir HBV)

Lamivudine has an additional black box warning regarding the need for HIV testing prior to therapy initiation and periodically during therapy. Lamivudine for HBV is given at a lower dose and less frequently than regimens used for the management of HIV. Emergence of lamivudine-resistant HIV strains is rapid due to the subtherapeutic dose, so lamivudine doses must be higher in HBV/HIV co-infected patients.

telbivudine (Tyzeka)

Cases of myopathy have been reported with telbivudine use, occurring weeks to months after starting therapy. Myopathy has also been reported with other drugs in this class.

Uncomplicated myalgia has been reported in clinical trials with telbivudine. Telbivudine therapy should be withheld if myopathy is suspected and discontinued if myopathy is diagnosed. Development of myopathy with telbivudine has not followed a pattern regarding the timing or creatine kinase elevation. Risk factors for creatine kinase elevations with telbivudine have not been identified at this time. Use of telbivudine with other drugs noted to increase the risk of myopathy should be done with caution. Muscle-related adverse effects incidence rates were two percent in both telbivudine and lamivudine groups in a clinical trial; however, creatine kinase elevations (\geq seven times upper limit of normal [ULN]) occurred in nine and three percent of the telbivudine and lamivudine groups, respectively.

Peripheral neuropathy has been reported with telbivudine; telbivudine therapy should be interrupted if peripheral neuropathy is suspected, and discontinued if confirmed. Risk is increased when telbivudine is given in combination with pegylated interferon alfa-2a (Pegasys) and other interferons. The safety and efficacy of telbivudine in combination with pegylated interferons or other interferons for the treatment of chronic HBV have not been demonstrated. Patients should be advised to report any numbness, tingling, and/or burning sensations in the arms and/or legs, with or without gait disturbance.

Drug Interactions^{75,76,77,78}

Adefovir (Hepsera), entecavir (Baraclude), and telbivudine (Tyzeka) are not substrates for CYP 450 enzyme systems nor do they inhibit the P450 system. No clinically significant drug interactions with telbivudine have been noted. Telbivudine elimination may be affected by drugs that reduce renal function.

Lamivudine (Epivir HBV) and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

Adefovir dipivoxil should not be used concurrently with tenofovir (Viread) or tenofovir-containing products such as emtricitabine/tenofovir disoproxil fumarate combination tablet (Truvada) and efavirenz/emtricitabine/tenofovir disoproxil fumarate combination tablet (Atripla).

Adverse Effects

Drug	Asthenia/ Malaise/ Fatigue	Headache	Abdominal pain	Nausea/ Vomiting	Diarrhea	ALT increase
adefovir dipivoxil (Hepsera) ⁷⁹ n=294 (placebo n=228)	13 (14)	9 (10)	9 (11)	5/nr (8)/nr	3 (4)	20 (41) (>5 X ULN)
entecavir 0.5 mg daily n=679	1	2	nr	< 1/< 1	< 1	2
entecavir 1 mg daily n=183 (Baraclude) ⁸⁰	3	4		< 1/< 1	1	2
lamivudine (EpiVir HBV)	1-3	1-2		< 1-2/0-< 1	0	4-11 (> 10 X ULN and > 2 x baseline)
lamivudine (EpiVir HBV) ⁸¹ n=332 (placebo n=200)	24 (28)	21 (21)	16 (17)	15 (17)	14 (12)	11 (13) (> 3 X baseline)
telbivudine (Tyzeka) ⁸² n=847	nr	10	3	5	7	5
lamivudine (EpiVir HBV) n=852	nr	11	4	5	5	8 (> 10 X ULN and > 2 X baseline)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Special Populations**Pediatrics**^{83,84,85,86}

Lamivudine (EpiVir HBV) is indicated for the treatment of chronic HBV in children ages two years and older.

Lamivudine was more effective than placebo in a randomized, double-blind, placebo-controlled trial with 287 children with chronic HBV and positive HBeAg.⁸⁷ Patients (ages two to 17 years) were randomized to lamivudine oral solution 3 mg/kg daily with a maximum dose of 100 mg daily or placebo for 48 weeks. Twenty-three percent of lamivudine patients achieved a virologic response, defined as the loss of HBeAg and undetectable HBV DNA levels, compared to only

13 percent of the placebo patients. Sustained ALT normalization occurred in 55 percent and 12 percent in the lamivudine and placebo groups, respectively ($p < 0.001$). Undetectable HBV DNA was seen in 61 percent of the lamivudine group and 16 percent of placebo patients ($p < 0.001$). Lamivudine was well tolerated in this group of children.

Adefovir (Hepsera) is indicated for the treatment of chronic HBV in children ages 12 to 17 years of age. The safety, efficacy, and pharmacokinetics of adefovir have been evaluated in a randomized, double-blind, placebo-controlled trial with 83 children between the ages of 12 and 17 years with chronic HBV and compensated liver disease.⁸⁸ The primary efficacy endpoints were the serum HBV DNA $< 1,000$ copies/mL and normal ALT levels at the end of 48 weeks. Twenty-three percent of the adefovir-treated patients achieved these endpoints compared to zero percent of the placebo-treated patients. In addition, of the children who were less than 12 years of age, the efficacy of adefovir was not significantly different from placebo. Therefore, adefovir is not recommended for use in children under age 12.

Safety and effectiveness of telbivudine (Tyzeka) in children with chronic HBV have not been established. Entecavir (Baraclude) has not been studied in children less than 16 years of age.

Pregnancy

Adefovir, entecavir, and lamivudine are Pregnancy Category C; telbivudine is Pregnancy Category B.

Co-Infections

Adefovir has been compared to tenofovir in patients co-infected with HBV and HIV-1 with 98 percent of patients having compensated liver disease.⁸⁹ In a randomized, double-blind, placebo-controlled trial, patients received either tenofovir 300 mg or adefovir 10 mg daily. Patients ($n=52$) were on stable antiretroviral therapy for HIV with HIV RNA levels of $\leq 10,000$ copies/mL (73 percent with HIV RNA < 50 copies/mL). HBV DNA levels were $\geq 100,000$ copies/mL at enrollment. At week 48, the mean time-weight average change in HBV DNA compared to baseline was -4.44 log copies/mL for tenofovir and -3.21 log copies/mL for adefovir. The study was terminated early at an interim review, as the primary noninferiority endpoint had been met without any safety issues. ALT elevations were similar in both groups.

Entecavir should not be administered to patients infected with both HIV and HBV unless the patient is already receiving HAART for HIV.

Telbivudine has not been well studied in populations with other concurrent viral infections including HIV, hepatitis C, or hepatitis D.

Renal Insufficiency

Dosage adjustments for renal impairment are necessary for all drugs in this category.

Hepatic Insufficiency

Adefovir has been approved for use in patients with decompensated liver disease with lamivudine-resistant HBV.

Single-dose pharmacokinetic data were evaluated for telbivudine in patients with mild to severe hepatic impairment without differences observed among the varying degrees of hepatic impairment.⁹⁰

No dosage or interval adjustment is required with entecavir, lamivudine, or telbivudine in hepatic insufficiency.

Transplantation

Currently, safety or efficacy data are not available for the use of telbivudine in patients with liver transplantation. Renal function should be monitored in patients with a liver transplant and concurrent immunosuppressants such as cyclosporine and tacrolimus when receiving adefovir or telbivudine.

Serum creatinine elevations of ≥ 0.3 mg/dL in pre- and post-transplant populations receiving adefovir have been reported in 37 and 53 percent of patients after weeks 48 and 96, respectively. Entecavir has not been well studied in the liver transplantation population.

In an open-label trial, patients (n=324) with lamivudine-resistant HBV were treated with adefovir 10 mg once daily.⁹¹ Patients were pre- (n=128) and post-liver transplantation (n=196). In patients who received 48 weeks of therapy, adefovir reduced HBV DNA to undetectable levels in 81 and 34 percent of the pre- and post-liver transplantation patients, respectively. The median duration of therapy for the pre- and post-transplantation groups was 18.7 weeks and 56.1 weeks, respectively. Normalization of ALT occurred in 76 percent of the pre-transplant group and 49 percent of the post-transplant group. Child-Pugh Turcotte score improved in over 90 percent of patients in both groups. No adefovir resistance was noted.

Race

Long-term use of lamivudine has been studied in a largely Asian population (98 percent Asian and 85 percent male) in one trial.⁹² Lamivudine 100 mg daily or placebo were evaluated in 651 patients with chronic hepatitis B with histologically confirmed cirrhosis or advanced fibrosis over a period of up to five years. The primary endpoint was the time to disease progression, defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices or death related to liver disease. The study was terminated after a median duration of treatment of 32.4 months due to a significant difference between treatment groups in the number of end points reached. End points were reached by 7.8 percent of the patients receiving lamivudine and 17.7 percent of those receiving placebo (hazard ratio for disease progression, 0.45; $p=0.001$). Hepatocellular carcinoma occurred in 3.9 percent of the lamivudine-treated group and 7.4 percent of the placebo-assigned group (hazard ratio, 0.49; $p=0.047$). Genotypic resistance YMDD mutations developed in 49 percent of the patients treated with lamivudine, and the Child–Pugh score was more likely to increase in patients with these mutations than in the other patients treated with lamivudine (seven percent versus less than one percent). The incidence and nature of adverse events were similar among patients who received lamivudine and those who received placebo.

Two randomized, double-blind placebo-controlled trials evaluated the safety and efficacy of adefovir dipivoxil 10 mg daily over 48 weeks in Asian (n=259) and Caucasian (n=242) patients with chronic HBV infection.⁹³ Patient populations included both HBeAg-positive and HBeAg-negative patients. After 48 weeks, histological improvement was observed in 60 and 40 percent of the Caucasian and Asian patients, respectively. The percentage of patients achieving undetectable HBV DNA (<400 copies/ml) at week 48 was similar (34 percent Caucasian; 39 percent Asian). The percentage of patients achieving normal ALT levels at week 48 was similar in both groups (Caucasian 64 percent, Asian 63 percent). No patients developed resistance through week 48. Adverse events were similar between the two groups. Authors concluded that there were no significant differences in treatment response between Asians and Caucasians.

Dosages

Drug/Availability	Adult Dose	Pediatric Dose	Adjustment for Renal Impairment
adefovir dipivoxil (Hepsera) ⁹⁴ 10 mg tablets	10 mg daily	10 mg daily (age ≥ 12 years)	CrCl ≥ 50 mL/min: 10 mg every 24 hours CrCl 30-49 mL/min: 10 mg every 48 hours CrCl 10-29 mL/min: 10 mg every 72 hours Hemodialysis: 10 mg every seven days following dialysis
entecavir (Baraclude) ⁹⁵ 0.5 and 1 mg tablets 0.05 mg/mL oral solution	(≥16 years old) 0.5 mg daily Known lamivudine or telbivudine resistance mutations: 1 mg daily Entecavir should be administered on an empty stomach either two hours before or after a meal.	--	<u>Renal impairment</u> CrCl 30-< 50 mL/min: 0.25 mg daily or 0.5 mg every 48 hours CrCl 10-< 30 mL/min: 0.15 mg daily or 0.5 every 72 hours CrCl<10 mL/min or hemodialysis/CAPD: 0.05 mg daily or 0.5 mg every seven days given after dialysis session <u>Renal impairment in lamivudine-refractory patients</u> CrCl 30- < 50 mL/min: 0.5 mg daily or 1 mg every 48 hours CrCl 10-< 30 mL/min: 0.3 mg daily or 1 mg every 72 hours CrCl<10 mL/min or hemodialysis/CAPD: 0.1 mg daily or 1 mg every seven days given after dialysis session
lamivudine (EpiVir HBV) ⁹⁶ 100 mg tablets 5 mg/mL oral solution	100 mg daily For HIV/HBV co-infection: 150 mg twice daily	3 mg/kg up to 100 mg daily (two to 17 years old)	CrCl 30-49 mL/min: 100 mg first dose then 50 mg daily CrCl 15-29 mL/min: 100 mg first dose then 25 mg daily CrCl 5-14 mL/min: 35 mg first dose then 15 mg daily CrCl<5 mL/min: 35 mg first dose then 10 mg daily No additional doses are necessary following hemodialysis
telbivudine (Tyzeka) ⁹⁷ 600 mg tablet 100 mg/5 mL oral solution	(≥16 years old) 600 mg daily	--	CrCl 30-49 mL/min: 600 mg every 48 hours CrCl<30 mL/min not on hemodialysis: 600 mg every 72 hours End Stage Renal Disease (ESRD): 600 mg every 96 hours; if given on hemodialysis days, give after session

All agents except where noted may be taken without regard for food.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and hepatitis B. Randomized, controlled comparative trials are considered the most relevant in this category; however, in the absence of comparative trials, placebo comparisons were considered. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the studies published for oral agents for treatment of chronic HBV infection are performed outside of the United States with several performed in Asia where chronic HBV infection is more common. Many of the published studies had small populations.

adefovir dipivoxil (Hepsera) in patients with lamivudine (Epivir HBV) resistance

The addition of adefovir dipivoxil to lamivudine in the presence of YMDD-mutant HBV was associated with improvement in patients with decompensated or compensated chronic HBV in a small trial.⁹⁸ Compensated chronic HBV-infected patients were randomized to adefovir 10 mg daily (n=46) or placebo (n=49) for 52 weeks in addition to ongoing lamivudine 100 mg daily. The patients with decompensated HBV or post-liver transplantation (n=40) were given adefovir plus lamivudine for 52 weeks. Response was defined as a decline in HBV DNA to 10⁵ copies/mL or a greater than two log reduction from baseline at week 48 to 52. In the compensated patients, adefovir was associated with a virologic response in 85 percent of patients compared to 11 percent with lamivudine alone (p<0.001) with a significant change from baseline occurring between the groups (median, -4.6 versus +0.3 log copies/mL, respectively, p<0.001). Normalization of ALT values occurred in 31 percent versus six percent for the adefovir/lamivudine and lamivudine groups, respectively (p=0.002). In the decompensated patients, 92 percent of patients had a median HBV DNA reduction of -4.6 log copies/mL and improved liver chemistries (p≤0.001). Therapy was well tolerated.

In a randomized, double-blind study in Hong Kong, lamivudine 100 mg daily plus placebo and lamivudine 100 mg daily plus adefovir dipivoxil 10 mg daily were compared in 115 HBeAg-positive patients with chronic HBV infection over 104 weeks.⁹⁹ Patients were treatment-naïve. Time-weighted average change in serum HBV DNA from baseline up to week 16 was -4.20 log₁₀ copies/mL for both groups (p=0.936). At week 104, median serum HBV DNA change from baseline (log₁₀ copies/mL) for monotherapy and combination therapy was -3.41 versus -5.22 percent, respectively. ALT normalization at week 104 was 34 percent (19/56) in the lamivudine monotherapy group and 45 percent (23/51) in the combination therapy group (p=0.018). By week 104, HBeAg seroconversion occurred in 20 percent of monotherapy and 13 percent of combination therapy patients. Both regimens were well tolerated.

entecavir (Baraclude) and lamivudine (Epivir HBV)

In a Phase III double-blind trial, 715 patients with HBeAg-positive chronic HBV infection were randomized to entecavir 0.5 mg daily or lamivudine 100 mg daily for a minimum of one year.¹⁰⁰ Patients had not previously received nucleoside analog therapy. After 48 weeks, histological improvement (defined as at least a two points decrease on Knodell necroinflammatory score) occurred in 72 and 62 percent of the entecavir and lamivudine groups, respectively ($p=0.009$). Significantly more patients achieved undetectable HBV DNA with entecavir (67 versus 36 percent, $p<0.001$). The entecavir group had a significantly greater reduction in the mean HBV DNA level from baseline compared to lamivudine at week 48 (-6.9 log copies/mL versus -5.4 log copies/mL, $p<0.001$). Normalization of ALT was reported in 68 and 60 percent of the entecavir and lamivudine groups, respectively ($p=0.02$). Seroconversion rates were similar in both groups with 21 percent of patients in the entecavir group and 18 percent in the lamivudine group ($p=0.33$). Both treatments were well tolerated with no reports of viral resistance to entecavir.

As a continuation of the Phase III study, at week 52, protocol-defined virologic responders could continue blinded treatment for up to 96 weeks.¹⁰¹ Patients continuing in year two (entecavir, $n=243$; lamivudine, $n=164$) were assessed for serum HBV DNA, ALT normalization, HBeAg seroconversion, and safety. Among patients treated in year two, 74 percent of entecavir-treated versus 37 percent of lamivudine-treated patients achieved HBV DNA <300 copies/mL by polymerase chain reaction (PCR). Normalized ALT levels occurred in 79 percent of entecavir-treated and 68 percent of lamivudine-treated patients. Seroconversions were achieved in 11 and 12 percent of entecavir- and lamivudine-treated patients, respectively. Higher proportions of entecavir-treated than lamivudine-treated patients achieved cumulative confirmed HBV DNA <300 copies/mL by PCR (80 percent versus 39 percent; $p<0.0001$) and ALT normalization (87 percent versus 79 percent; $p=0.0056$) through 96 weeks. Cumulative confirmed HBeAg seroconversion occurred in 31 percent of entecavir-treated versus 25 percent of lamivudine-treated patients ($p=NS$). Through 96 weeks, no patient experienced virologic breakthrough due to entecavir resistance. The safety profile was comparable in both groups.

In a similarly designed double-blind trial, patients ($n=648$) with HBeAg-negative chronic HBV infection were randomized to entecavir 0.5 mg daily or lamivudine 100 mg daily for at least one year in the Phase III study.¹⁰² During the trial, conducted in nucleoside analog treatment-naïve patients, histological improvement was observed in 70 and 61 percent of patients on entecavir and lamivudine, respectively ($p=0.01$). Normalization of ALT occurred in 78 and 71 percent of the entecavir and lamivudine groups, respectively ($p=0.045$). Undetectable HBV DNA was reported more frequently with entecavir than lamivudine (90 versus 72 percent, $p<0.001$). Entecavir had a significantly greater mean reduction in HBV DNA compared to baseline than lamivudine (-5.0 versus -4.5 log copies/mL, $p<0.001$). No viral resistance was reported with entecavir. Both therapies were well tolerated.

Switching to entecavir or continuing on lamivudine treatment was evaluated in 286 patients with HBeAg-positive chronic HBV infection with either persistent viremia or documented YMDD mutations while receiving lamivudine.¹⁰³ Therapies were compared at 48 weeks for histologic improvement and HBV DNA viral load reduction with ALT normalization (less than 1.25 times the upper limit of normal). Histologic improvement occurred in 55 percent (68/124) of entecavir-treated versus 28 percent (32/116) of lamivudine-treated patients ($p<0.0001$) after 48 weeks. More patients on entecavir than lamivudine achieved the composite end point: 55 percent (77/141) versus four percent (6/145), respectively ($p<0.0001$). Virologic rebound occurred in 2 of 141 entecavir-treated patients. Adverse effects of entecavir were comparable to lamivudine with fewer ALT flares on treatment.

The efficacy, safety, and resistance profiles of entecavir through 96 weeks of treatment were evaluated in 141 treated-patients with virologic response at 52 weeks (defined as HBV DNA < 0.7 mEq/mL, but HBeAg-positive).¹⁰⁴ Patients continued treatment with entecavir 1 mg daily or continued lamivudine 100 mg daily. Between week 48 and the end of entecavir dosing, the proportions of patients with HBV DNA <300 copies/mL increased from 21 percent to 40 percent ($p<0.0001$), HBeAg seroconversion increased from zero percent to 16 percent ($p=0.012$), and ALT normalization (\leq one-times the upper limit of normal) increased from 65 percent to 81 percent ($p<0.0001$). In the second year, HBeAg seroconversion was achieved by 10 percent of patients. Of the 77 patients in the second-year treatment cohort, entecavir resistance emerged in six patients, and seven experienced virologic breakthrough. The safety profile of entecavir was similar to that of the first year of treatment.

telbivudine (Tyzeka) and lamivudine (Epivir HBV)

The randomized, double-blind GLOBE study compared safety and efficacy of telbivudine 600 mg daily and lamivudine 100 mg daily in 1,370 nucleoside analog treatment-naïve patients with compensated chronic HBV.^{105,106,107} All patients enrolled in the trial had evidence of viral replication indicated by HBsAg-positive status, either HBeAg-positive or -negative status, detectable HBV DNA and elevated ALT levels (≥ 1.3 times ULN) as well as chronic inflammation on liver biopsy. The primary efficacy endpoint was noninferiority of telbivudine to lamivudine for therapeutic response based on reduction in serum HBV DNA levels to fewer than five log₁₀ copies/mL, along with normalization of ALT levels or loss of detectable serum HBeAg. Secondary efficacy endpoints included improvement of liver histology, serum HBV DNA changes, normalization of serum alanine aminotransferase levels, HBeAg and HBsAg loss and seroconversion. At week 52 in the HBeAg-positive patients, 75.3 percent of patients achieved suppression of HBV DNA to less than 5 log₁₀ copies/mL with either a loss of HBeAg or ALT normalization ($p=0.005$). In the lamivudine group, 67 percent of patients achieved the same response. At week 52, a significantly higher proportion of HBeAg-positive patients receiving telbivudine than of those receiving lamivudine had a histologic response (64.7 percent versus 56.3 percent, $p=0.01$). Telbivudine was also non-inferior to lamivudine for these endpoints in HBeAg-negative patients. At week 52, the mean HBV DNA reduction was -6.45 log copies/mL in the telbivudine group and -5.54 log copies/mL in the lamivudine group; the difference was statistically significant. After 52 weeks, loss of HBeAg was not significantly different between the two treatment groups (telbivudine, 26 percent versus lamivudine, 23 percent). In the HBeAg-negative patients, 75 and 77 percent of the telbivudine and lamivudine patients achieved the therapeutic response, respectively ($p=0.62$). At week 52, the mean HBV DNA reduction was -5.23 log copies/mL in the telbivudine group and -4.40 log copies/mL in the lamivudine group in the HBeAg-negative group ($p<0.05$). In the HBeAg-positive patient population, treatment-emergent HBV resistance was three percent at week 48 for telbivudine patients compared to 8.2 percent for lamivudine patients ($p=0.0007$). In the HBeAg-negative patient population, similar results of HBV resistance were seen after 48 weeks of therapy with 2.1 percent of telbivudine patients and 8.5 percent of lamivudine patients having HBV resistance ($p<0.01$). Elevated creatinine kinase levels were more common in patients receiving telbivudine, whereas elevated ALT and AST levels were more common in patients receiving lamivudine. This study was co-sponsored by the manufacturer of telbivudine.

Patients were followed in the GLOBE trial until week 104.^{108,109} In the HBeAg-positive patients, telbivudine had significantly greater responses, defined as HBV DNA less than 5 log₁₀ copies/mL and either HBeAg loss or normalization of ALT level, than lamivudine (63 versus 48 percent, respectively; $p<0.001$). In the HBeAg-positive group, telbivudine also had significantly greater percentages of patients with undetectable HBV DNA (56 versus 39 percent; $p<0.001$)

and ALT normalization (70 versus 62 percent; $p < 0.05$). Mean HBV DNA reductions (-5.7 versus -4.4 log copies/mL) were greater in the HBeAg-positive group receiving telbivudine compared to lamivudine. In the HBeAg-negative patients, significantly more patients achieved a therapeutic response with telbivudine (78 versus 66 percent; $p < 0.007$). While significantly more patients achieved undetectable HBV DNA (82 versus 57 percent; $p < 0.001$) with telbivudine than lamivudine, ALT normalization (78 versus 70; $p = \text{NS}$) was similar for both groups. Telbivudine was associated with a greater mean reduction in HBV DNA (-5.0 versus -4.2 log copies/mL; $p < 0.05$). HBV resistance was significantly greater in the lamivudine group at week 104 with 25.9-39.5 percent compared to telbivudine resistance rates of 10.8-25.1 percent (both $p < 0.001$). The study suggested lower serum HBV DNA levels (or undetectable HBV DNA levels) at week 24 predicted a higher likelihood of HBeAg conversion, undetectable HBV DNA levels, and normalized ALT at week 52.

In a randomized, double-blind trial, telbivudine and lamivudine and the combination were compared in 104 patients with HBeAg-positive adults with compensated chronic HBV.¹¹⁰ Patients were randomized to telbivudine 400 or 600 mg daily, telbivudine 400 or 600 mg daily plus lamivudine 100 mg daily, or lamivudine 100 mg daily. After 52 weeks, median reductions of HBV DNA were -4.66 log copies/mL for lamivudine, -6.43 log copies/mL for telbivudine 400 mg, -6.09 log copies/mL for telbivudine 600 mg, -6.40 log copies/mL for lamivudine/telbivudine 400 mg, and -6.05 log copies/mL for lamivudine/telbivudine 600 mg. In comparing monotherapies, telbivudine was associated with a greater mean reduction in HBV DNA levels (-6.05 versus -4.57 log copies/mL, $p < 0.05$), greater percent of patients with undetectable HBV DNA (61 percent versus 32 percent, $p < 0.05$) and the normalization of ALT (86 versus 63 percent, $p < 0.05$) compared to lamivudine. Both monotherapy groups had similar rates of HBeAg seroconversion (31 versus 22 percent, $p = \text{NS}$). Combination therapy did not provide additional benefits beyond those seen with telbivudine. All therapies were well tolerated.

A Phase III, double-blind, randomized, multicenter trial in 332 Chinese patients with compensated HBeAg-positive ($n = 290$) and HBeAg-negative ($n = 42$) patients was conducted to compare the efficacy of telbivudine 600 mg to lamivudine 100 mg over 104 weeks.¹¹¹ The primary efficacy endpoint was reduction in serum HBV DNA levels at week 52 of treatment. Secondary endpoints included clearance of HBV DNA to undetectable levels, HBeAg loss and seroconversion, therapeutic response, and ALT normalization. At week 52, amongst the HBeAg-positive patients, there was a significantly greater reduction in serum HBV DNA in telbivudine-treated patients versus lamivudine-treated patients (-6.3 log₁₀ versus -5.5 log₁₀, $p < 0.001$). In addition, the telbivudine group more commonly showed ALT normalization (87 percent versus 75 percent, $p = 0.007$), therapeutic response (85 percent versus 62 percent, $p = 0.001$), and HBeAg loss (31 percent versus 20 percent, $p = 0.047$). Treatment effects showed similar patterns in the smaller HBeAg negative group. Viral resistance in telbivudine patients was not statistically different from the lamivudine treated group. Clinical adverse effects were similar in the two groups. In summary, telbivudine treatment for 52 weeks provided greater antiviral and clinical efficacy than lamivudine in Chinese patients with chronic hepatitis B.

Summary

Two groups have developed treatment recommendations for the management of chronic hepatitis B. The AASLD 2009 guidelines list the first-line drugs for the treatment of chronic hepatitis B as peginterferon alfa-2a (Pegasys), entecavir (Baraclude), and tenofovir (Viread). Due to the high rate of drug resistance during long term treatment, lamivudine (Epivir HBV) and telbivudine (Tyzeka) are not preferred treatments for chronic hepatitis B except when only a short course of treatment is planned. Adefovir (Hepsera) is less potent than the other oral

antivirals, and it is associated with increasing viral resistance rates after the first year of therapy and risk of nephrotoxicity. Adefovir (Hepsera) is a second-line agent for treatment-naïve patients. In the 2008 treatment algorithm, the preferred first-line treatment choices are entecavir (Baraclude), peginterferon alfa-2a (Pegasys), and tenofovir (Viread). Issues for consideration for therapy according to the 2008 treatment algorithm include efficacy, safety, rate of resistance, method of administration, and cost.

Entecavir (Baraclude) has been shown to be effective, at a higher daily dose, in patients with documented lamivudine-resistant strains of HBV. In treatment-naïve patients with chronic HBV, entecavir resistance has been rarely reported. Entecavir (Baraclude) is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy HAART.

Lamivudine (Epivir HBV) is a well-tolerated oral medication that is efficacious and approved for use in children; however, viral resistance hinders its clinical success over time. Resistance has also been reported in up to 25 percent of patients on telbivudine (Tyzeka) over two years.

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