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Class Update: Antivirals for Hepatitis B

Date of Review: March 2017 **Date of Last Review:** March 2014

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: To identify and evaluate new comparative evidence for the safety and efficacy of medications used in the treatment of Hepatitis B virus (HBV) and review updated guidelines since the last class review was published.

Research Questions:
1. Is there new evidence demonstrating differences in efficacy or effectiveness between antivirals for the treatment of HBV?
2. Is there new evidence demonstrating differences in the safety of antivirals for the treatment of HBV?
3. Are there specific populations (e.g. pregnancy) in which one antiviral may be more effective or safer for the treatment of HBV?

Conclusions:
- There is limited, low-quality evidence suggesting greater efficacy of entecavir over lamivudine and adefovir.
- There is no difference in terms of efficacy or safety between entecavir and tenofovir. Both antiviral agents are recommended as first-line treatments by consensus guidelines.
- There is no difference in efficacy between tenofovir, lamivudine, and telbivudine in reducing perinatal transmission during pregnancy. According to consensus guidelines, safety evidence for tenofovir and lamivudine is demonstrated through outcomes in Antiretroviral Pregnancy Registry.
- One randomized trial showed tenofovir had favorable outcomes in treatment of HBV in known-lamivudine resistant patients. Switching to tenofovir is recommended by guidelines in cases of known resistance to other antiviral agents.
- There is insufficient evidence of improved efficacy or effectiveness or safety of tenofovir alafenamide compared to other antivirals for the treatment of HBV.

Recommendations:
- Maintain at least one of the guideline-recommended first line treatments, tenofovir and entecavir, as preferred agents on the PDL. Compare costs in executive session for cost comparison.
- Add tenofovir alafenamide to Preferred Drug List as a non-preferred antiviral.
- Revise prior authorization criteria as follows:
    - Add pediatric indication for telbivudine
    - Update recommendations for undetectable HBV DNA as defined by consensus guidelines below 10 IU/ml

Author: Melissa Smith, PharmD Date: March 2017

Previous Conclusions and Recommendations:

- Evidence does not support a difference in efficacy/effectiveness or in harms/adverse events between antiviral agents for Hepatitis B.
- Lamivudine has the most robust long-term safety data and still has a place in therapy in those with favorable parameters and low risk of resistance. It can also be recommended in clinical situations which a finite prophylaxis course is needed.
- Consensus guidelines recommend either tenofovir or entecavir as first line antivirals for the treatment of hepatitis B. Maintain tenofovir as a preferred hepatitis B antiviral and make entecavir non-preferred based on no clinical evidence of superiority of one agent over the other.
- Establish prior authorization criteria for the non-preferred agents in this class to promote the use of the preferred products.

Background:

Hepatitis B infection caused by the hepatitis B virus (HBV), can be defined as either acute or chronic disease.[1] It is estimated approximately 850,000 persons have chronic hepatitis B (CHB) in the United States, and may be up to 2.2 million including foreign-born persons.[2,3] HBV is transmitted through percutaneous or mucosal exposure to blood or bodily fluids of an infected person. Once a person is infected, HBV infection can be either asymptomatic or symptomatic and can progress into a chronic disease.[4] The risk of developing CHB depends on the age at which the individual becomes infected, with the majority of chronic infection developing in those initially infected in infancy and childhood.[4] Approximately 90% of infants infected with HBV in the perinatal period will develop CHB, whereas only 5% of adults acutely infected develop CHB.[1] The early identification of infected individuals, prevention through vaccination, and treatment of those infected with HBV can reduce morbidity and mortality of CHB.[5]

The diagnosis of hepatitis B is based on clinical examination and serologic testing. Hepatitis B surface antigen (HBsAg) in the blood gives a diagnosis of hepatitis B infection. Routine assessment of additional serologic markers, such as HBV DNA, hepatitis B "e-antigen" (HBeAg), and alanine aminotransferase (ALT) levels, should be performed in order to guide the management of hepatitis B. Additional testing to determine the advancement of liver fibrosis through non-invasive tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest is also recommended.[1]

Chronic hepatitis B is defined as having detectable levels of HBsAg in the blood for greater than 6 months.[1] Due to the dynamic nature of CHB, there have been different phases of disease described in literature. The phases are of variable duration and are not sequential. Not every person infected can be described in a specific phase and treatment will not always correlate to a specific phase.[1, 5] The phases are described in **Table 1**.

Table 1. Phases of Chronic Hepatitis B[5]

Phase	HBV DNA	ALT	HBeAg status
Immune-tolerant phase	Elevated, typically >1 million IU/mL	Normal	Positive
HBeAg-positive immune-active phase	Elevated, ≥20,000 IU/mL	Elevated[†]	Positive
Inactive CHB phase	Low or undetectable, <2,000 IU/mL	Normal	Negative
HBeAg-negative immune reactivation phase	Elevated, ≥2,000 IU/mL	Elevated[†]	Negative

[†]Elevated ALT defined at >2 times upper limit of normal (ULN) (normal ALT 30 U/L for males, 10 U/L for females)

Although most patients with CHB will not develop liver-related complications, the 5-year incidence of cirrhosis is approximately 8-20%, with relatively few of these cases developing hepatocellular carcinoma (HCC) (2-5%).[5] Deaths from cirrhosis and HCC were estimated to be 310,000 and 340,000 per year, worldwide.[5] Additional risk factors for developing cirrhosis and HCC in patients with CHB, include high serum HBV DNA (>2,000 IU/mL), elevated ALT levels, prolonged time to HBeAg seroconversion and development of HBeAg-negative CHB.[5]

Current antiviral therapy for CHB does not eradicate the virus, but can produce an immunological cure, defined as loss of HBsAg from the serum and sustained HBV DNA suppression. The goal of therapy is to reduce the incidence of liver-related complications including cirrhosis and hepatocellular carcinoma in patients with CHB.[6] The available treatment options for CHB include pegylated interferon or nucleoside/nucleotide analogs (NAs).[5] The American Association for the Study of Liver Diseases (AASLD) guidelines recommend the use of pegylated interferon, entecavir, or tenofovir as first line treatment, however for the purpose of this class review, only evidence relating to NAs will be evaluated. The available NAs are described in **Table 2.** Lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate require dose adjustment for creatinine clearance less than 50 mL/min.

Table 2. Nucleoside/Nucleotide Analogs (NAs) Approved for Treatment of Hepatitis B[5–7]

Drug	Adult Dose	Pediatric Dose	Severe adverse effects	Resistance Patterns
Lamivudine	100 milligram (mg) daily	Age ≥2 years: 3 mg/kilogram (kg) daily up to max 100 mg/day	Pancreatitis, lactic acidosis	Lamivudine resistance occurs in 16-32% in first year, up to 60-70% after 5 years of treatment
Adefovir dipivoxil	10 mg daily	Age ≥12 years: 10 mg daily	Acute renal failure, Fanconi syndrome, lactic acidosis	Occurs in 20-29% after 5 years of treatment
Telbivudine	600 mg daily	Age ≥16 years: 600 mg daily	Myopathy, peripheral neuropathy, lactic acidosis	Lower rate of resistance compared to lamivudine; mutations are cross-resistant with lamivudine
Entecavir	0.5 mg daily; 1 mg daily in lamivudine/ telbivudine-experienced patients or decompensated cirrhosis	Age ≥2 years: weight based dosing from 10-30 kg; >30 kg 0.5 mg daily	Lactic acidosis	Very low resistance pattern (<1% at one year, 1.2% at 5 years)
Tenofovir	300 mg daily (tenofovir disoproxil fumarate) 25 mg daily (tenofovir alafenamide)	Age ≥12 years: 300 mg daily (tenofovir disoproxil fumarate) Not approved in pediatrics (tenofovir alafenamide)	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	No resistance detected through 96 weeks of treatment

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and

Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

One new systematic review and meta-analysis was identified comparing antiviral therapy and interferon therapy for the treatment of CHB. A total of 73 studies were included, with 59 studies (15 RCTs and 44 observational studies) reporting clinical outcomes.[8] Evaluation using the assessment of multiple systematic reviews (AMSTAR) tool determined this was a high quality systematic review. The Cochrane Risk of Bias assessment tool, for RCTs, and the modified Newcastle-Ottawa Scale, for observational studies, were used to assess the risk of bias.[8] The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[8] For the purpose of this class review, only outcomes relating to NAs will be discussed. Only one observational study in patients with compensated cirrhosis measured all-cause mortality and demonstrated a reduction in all-cause mortality with entecavir compared to lamivudine (RR=0.4, 95% Confidence Interval (CI) 0.3-0.6), which was determined to be very low-quality evidence given the high risk of bias associated with the design of the study.[8] In decompensated cirrhosis, one RCT showed reduced risk of HCC with entecavir compared to adefovir (RR=0.4, 95% CI 0.2-0.8, moderate-quality evidence) and entecavir significantly reduced all-cause mortality versus lamivudine in one observational study with very low-quality evidence (RR=0.4, 95% CI 0.3-0.7).[8] Low-quality evidence from two observational studies suggested increased risk of viral relapse in those who stopped antiviral therapy compared to those who continued therapy following HBeAg seroconversion (RR=94.4, 95% CI 13.3-670.0, I^2=0%).[8] The overall conclusion of this systematic review was entecavir and tenofovir are preferred NAs given their potent antiviral activity and low risk of resistance in those with immune-active CHB, based on low-moderate quality evidence from observational studies.[8] There was little outcomes data in patients with advanced disease and limited evidence in regards to duration of therapy. No significant difference in safety profiles of entecavir and tenofovir was found.[8]

Another systematic review compared the safety and efficacy of tenofovir and entecavir in CHB.[9] A total of 2 RCTs, 4 cohort studies, and 1 case-cohort study were included (n=844).[9] The systematic review was determined to be high quality using the AMSTAR tool. Methodological quality of the RCTs was assessed using the Quality of Reporting of Meta-Analyses (QUOROM) guidelines and the JADAD scale.[9] The included non-RCTs were case matched, had well-defined inclusion and exclusion criteria, and a clear definition of treatment response.[9] No significant difference was found between tenofovir and entecavir in terms of HBV DNA suppression (6 studies included) and ALT normalization (4 studies included) at 48 weeks.[9] Tenofovir had an HBV DNA suppression rate of 80% at 48 weeks, compared to 76% for entecavir (RR=1.07, 95% CI 0.99-1.17).[9] ALT normalization occurred in 74% of the tenofovir group compared to 81% in the entecavir group (RR=0.91, 95% CI 0.83-1.01).[9] HBeAg seroconversion rates at 48 weeks were compared in 4 studies and found no difference between tenofovir (16%) and entecavir (10%) (RR=1.09, 95% CI=0.57-2.11).[9] There was no difference in terms of adverse effects related to the two agents.[9] Entecavir and tenofovir were found to be comparable in terms of efficacy and safety, however, there was a limited number of studies (7 included) comparing the two agents, with the majority being non-RCTs (5 of 7 studies), and analysis was underpowered for some indicators.[9] Therefore, more long term studies with larger sample size are needed to confirm the results of this meta-analysis.

A systematic review and meta-analysis sought to determine efficacy and safety of antiviral therapy in pregnancy.[10] It included 10 RCTs and 16 non-randomized studies in 3622 pregnant women with CHB.[10] The Cochrane Risk of Bias assessment tool and Newcastle-Ottawa Scale were used to assess the risk of bias and the

quality of evidence was evaluated using the GRADE approach.[10] Five of the RCTs were determined to have high risk of bias due to unclear/unreported method of randomization, allocation concealment, blinding, or incomplete data reporting, while the other 5 RCTs had low risk of bias.[10] Oral antiviral therapy was compared to no therapy in HBeAg-positive women with high viral load (200,000 IU/mL) in regards to infant HBsAg seropositivity (8 RCTs) and infant HBV DNA positivity (5 RCTs).[10] Low to moderate-quality evidence showed antiviral therapy reduced infant HBsAg seropositivity (RR=0.3, 95% CI 0.2-0.4) and infant HBV DNA positivity (RR=0.3, 95% CI 0.2-0.5) at 6-12 months.[10] No difference was seen in infant HBsAg seropositivity at 6-12 months when comparing lamivudine versus telbivudine (RR=1, 95% CI 0.7-1.5) or tenofovir (RR=2.93, 95% CI 0.12-70.08).[10] Maternal outcomes evidence was very low-quality due to lack of evidence and imprecision. One cohort showed pregnant women treated with telbivudine, compared to lamivudine, had greater HBV DNA suppression at delivery (RR=1.8, 95% CI 1.3-2.6).[10] The benefit of antiviral therapy in immune-tolerant women is still unproven.[10]

New Guidelines:

Guidelines from the World Health Organization (WHO) [1]

The WHO published their guidelines focused on the prevention, care, and treatment of persons with chronic hepatitis B in March 2015.[1] The guidelines were developed in response to a lack of guidance for treating persons with CHB in low- and middle-income countries (LMICs), however the recommendations are also relevant to high-income countries.[1] The WHO guidelines address who to treat, recommendations for first and second-line therapies, when to stop treatment, and management of CHB in special populations.[1]

The guidelines recommend that:

- All persons with CHB and evidence of compensated or decompensated cirrhosis, should be treated as a priority (regardless of ALT level, HBeAg status, or HBV DNA level) (Strong recommendation, moderate quality of evidence).[1]
- Adults age >30 years old without evidence of cirrhosis, if they have persistently abnormal ALT levels and elevated HBV DNA >20,000 IU/mL should be treated (Strong recommendation, moderate quality of evidence).[1]
- Tenofovir or entecavir are first-line therapy in adults, due to the high barrier of drug resistance, with entecavir being recommended in children aged 2 to 11 years (Strong recommendation, moderate quality of evidence).[1]
- Therapy should be switched to tenofovir if antiviral resistance to lamivudine, entecavir, adefovir, or telbivudine is confirmed or suspected (Strong recommendation, low quality of evidence).[1]
- All persons with cirrhosis continue antiviral therapy lifelong, due to the risk of HBV reactivation causing liver complications (Strong recommendation, low quality of evidence).[1]
- NA therapy discontinuation can be considered in persons who meet the following criteria: no evidence of cirrhosis, can be followed long term for reactivation, evidence of HBeAg loss and conversion to anti-HBe with an additional one year of treatment, persistently normal ALT levels, and undetectable HBV DNA levels (Conditional recommendation, low quality of evidence).[1]
- The guidelines do recommend retreatment with antiviral therapy in cases of reactivation (HBsAg or HBeAg become positive, increase in ALT levels, or detectable HBV DNA) (Strong recommendation, low quality of evidence).[1]

The recommendations on when to treat pregnant women are the same as for other adults.[1] The preferred antiviral therapy is tenofovir based on safety data in HBV-infected pregnant women from the Antiretroviral Pregnancy Registry.[1]

Guidelines from the American Association for the Study of Liver Diseases (AASLD) [5]

The AASLD issued practice guidelines for the treatment of chronic hepatitis B in August 2015.[5] The guideline committee evaluated the evidence using the GRADE approach and summarized the quality of the evidence. Recommendations were based on quality of evidence, benefits and harms, patients' preferences, and clinical context.[5] The guideline recommendations are summarized in **Table 3**.

Table 3. Summary of AASLD Guideline Recommendations[5]

Recommendation	Quality of Evidence	Strength of Recommendation
Treatment of Persons with Immune-Active CHB		
Treat with antiviral therapy, regardless of HBeAg status	Moderate	Strong
Pegylated interferon (Peg-IFN), entecavir, or tenofovir as preferred initial therapy	Low	Strong
Treatment of Persons with Immune-Tolerant CHB		
No treatment recommended for most	Moderate	Strong
Consider treatment if >40 years old, HBV DNA ≥1,000,000 IU/mL, and liver biopsy showing fibrosis	Very Low	Conditional
Treatment of CHB in Pregnancy		
Treatment is recommended in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL	Low	Conditional
No treatment in pregnant women with HBV DNA ≤200,000 IU/mL	Low	Strong

Immune-active CHB is defined as ALT elevation of >2 times the ULN in addition to elevated HBV DNA >2,000 IU/mL in HBeAg negative or >20,000 IU/mL in HBeAg positive.[5] Therapy is recommended by the AASLD guidelines for all persons with immune-active CHB.[5] Additionally, therapy is recommended for all persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level. Additional factors that may be considered increased risk are age 40 years and older, family history of HCC, and presence of extrahepatic manifestations.[5] Antiviral therapies are similar in reducing the risk of liver-related complications with head-to-head comparisons failing to show superiority of one agent over another.[5] Peg-IFN, tenofovir, and entecavir are considered the preferred therapies largely due to lack of resistance with long-term use.[5] Length of NA therapy is variable, in some cases indefinite therapy is warranted. Factors to consider in determining duration of therapy include HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis/decompensation.[5]

The AASLD guidelines recommend against antiviral therapy in those with immune-tolerant CHB, defined as ALT ≤30 U/L for men and ≤19 U/L for women.[5] The guidelines do suggest therapy in adults >40 years of age, HBV DNA ≥1,000,000 IU/mL, and liver biopsy showing significant necroinflammation or fibrosis.[5] Those with immune-tolerant CHB should have ALT levels tested at least every 6 months to monitor for potential transition to immune-active or immune-inactive CHB (Quality of evidence: Very low, Strength of recommendation: Conditional).[5]

In HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on therapy, AASLD guidelines suggest discontinuing NA therapy after a period of treatment consolidation.[5] The period of consolidation includes continuing treatment for at least 12 months with persistently normal ALT levels and

undetectable HBV DNA.[5] However, an alternative approach would be to treat until serum HBsAg loss.[5] Indefinite antiviral therapy is recommended in all HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on NA therapy, due to concerns for decompensation and potential death.[5] Indefinite antiviral therapy is recommended in adults with HBeAg-negative immune-active CHB (Quality of evidence: Low, Strength of recommendation: Conditional).[5]

AASLD recommends treatment to reduce the risk of perinatal transmission in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL.[5] Tenofovir, lamivudine, and telbivudine are the only antivirals that have been studied in pregnancy, however the guidelines do not recommend one agent over another.[5]

New Safety Alerts:
None

New Formulations or Indications:
Vemlidy® (tenofovir alafenamide) was FDA approved for treatment of CHB infection in November 2016.[11] It is a nucleotide analog reverse transcriptase inhibitor and prodrug of tenofovir, similar to that of tenofovir disoproxil fumarate.[11] Tenofovir alafenamide has shown greater plasma stability compared to tenofovir disoproxil fumarate which allow for lower doses of tenofovir alafenamide to be efficacious.[12] The efficacy and safety of tenofovir alafenamide was studied in two randomized, double-blind, active-controlled, Phase 3 clinical trials, Study 108 and Study 110.[11] Tenofovir alafenamide 25 mg daily was compared to tenofovir disoproxil fumarate 300 mg daily in HBeAg-negative subjects in Study 108 (n=425) and in HBeAg-positive subjects in Study 110 (n=873).[11] They included both treatment-naïve and treatment-experienced subjects with compensated liver disease.[11] The efficacy endpoint in both trials was the proportion of subjects with plasma HBV DNA levels < 29 IU/mL at Week 48.[11] At week 48, both studies showed tenofovir alafenamide was statistically non-inferior to tenofovir disoproxil fumarate, with treatment difference of 1.8% (95% CI -3.6%-7.2%) in Study 108 and -3.6% (95% CI -9.8%-2.6%) in Study 110.[11] There was no significant difference in discontinuations due to adverse reactions between the two groups, in either of the studies.[11] In a combined analysis of Study 108 and Study 110, there was a statistically significant difference in change from baseline estimated glomerular filtration rate using Cockcroft-Gault ($eGFR_{CG}$) with tenofovir disoproxil fumarate at week 72 compared to tenofovir alafenamide (-4.2 mL/min vs. -0.6 mL/min, P<0.001).[12] A smaller decrease in bone mineral density in the hip (-2.43% vs -0.29%) and spine (-2.52% vs. -0.6%) at week 72 was also observed (P<0.001).[12]

Vemlidy is dosed at 25 mg once daily and is recommended to be taken with food.[11] Tenofovir alafenamide does not require dosage adjustment in patients with creatinine clearance (CrCl) 15-50 mL/min, compared to tenofovir disoproxil fumarate which requires dose adjustment with CrCl < 50 mL/min.[12] It is not recommended for use in patients with creatinine clearance less than 15 mL/min or those with severe hepatic impairment.[11] Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp), which effects bioavailability of the drug, therefore drugs that strongly effect P-gp will alter absorption of tenofovir alafenamide.[11] Common adverse reactions are similar to tenofovir disoproxil fumarate, which includes headache, fatigue, abdominal pain, cough, and back pain.[11]

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the literature search. After manual review, 19 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in **Table 4**. Full abstracts are included in

Table 4: Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Fung, et al.[13] DB, MC	TDF 300 mg once daily vs. FTC/TDF 200/300 mg once daily x 240 weeks	CHB (positive HBsAg test for ≥6 months) with HBV DNA ≥3000 IU/mL and confirmed LAM resistance (n=280)	Suppressed plasma HBV DNA (<69 IU/mL) at 96 weeks	89.4% in TDF group (n=141) vs. 86.3% in FTC/TDF group (n=139) (P=0.43) *HBeAg positive*: 84.6% in TDF group vs. 82.4% in FTC/TDF group (P=0.73) *HBeAg negative*: 93.4% in TDF group vs. 90% in FTC/TDF group (P=0.53)

Abbreviations: DB=Double blind; MC = Multi-center; TDF= tenofovir; FTC/TDF= emtricitabine + tenofovir; CHB= chronic hepatitis B; HBsAg= hepatitis B surface antigen; HBV= hepatitis B virus; LAM= lamivudine

References:

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10. Brown RSJ, McMahon BJ, Lok ASF, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. [Review]. *Hepatology*. 2016;63(1):319-333. doi:10.1002/hep.28302.

11. Vemlidy package insert. https://www.gilead.com/~/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.pdf?la=en. Accessed January 9, 2017.

12. Vemlidy® (tenofovir alafenamide) Formulary Dossier. 2017.

13. Fung S, Kwan P, Fabri M, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2014;146(4):980-988. doi:10.1053/j.gastro.2013.12.028.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SOLUTION	EPIVIR HBV	LAMIVUDINE	Y
ORAL	TABLET	EPIVIR HBV	LAMIVUDINE	Y
ORAL	TABLET	LAMIVUDINE	LAMIVUDINE	Y
ORAL	TABLET	LAMIVUDINE HBV	LAMIVUDINE	Y
ORAL	TABLET	VIREAD	TENOFOVIR DISOPROXIL FUMARATE	Y
ORAL	POWDER	VIREAD	TENOFOVIR DISOPROXIL FUMARATE	N
ORAL	SOLUTION	BARACLUDE	ENTECAVIR	N
ORAL	TABLET	ADEFOVIR DIPIVOXIL	ADEFOVIR DIPIVOXIL	N
ORAL	TABLET	BARACLUDE	ENTECAVIR	N
ORAL	TABLET	ENTECAVIR	ENTECAVIR	N
ORAL	TABLET	HEPSERA	ADEFOVIR DIPIVOXIL	N
ORAL	TABLET	TYZEKA	TELBIVUDINE	N
ORAL	TABLET	VEMLIDY	TENOFOVIR ALAFENAMIDE	N

Appendix 2: Abstracts of Clinical Trials

1. Fung S, Kwan P, Fabri M, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2014;146(4):980-988.

Background & Aims: Tenofovir disoproxil fumarate (TDF) is active against lamivudine-resistant hepatitis B virus (HBV) infection, but data to support its clinical efficacy in this setting are limited.
Methods: In a prospective, double-blind, 96-week trial, patients were randomly assigned (1:1) to groups given TDF (300 mg, n = 141) or a combination of emtricitabine (FTC, 200 mg; n = 139) and TDF (300 mg, FTC/TDF). Patients were hepatitis B e antigen (HBeAg)−positive or HBeAg-negative, with levels of HBV DNA ≥3 log10 IU/mL and lamivudine resistance mutations (HBV polymerase or reverse transcriptase amino acid substitutions rtM204I/V ± rtL180M by INNO-LiPA Multi-DR v3; Innogenetics, Inc, Alpharetta, GA). The primary end point was proportion with HBV DNA <69 IU/mL (Roche COBAS Taqman assay; Roche Molecular Systems, Inc, Pleasanton, CA).
Results: Patient groups were well matched for demographic and disease characteristics, including region (60% from Europe), HBV genotype (45% genotype D), HBeAg status (47% HBeAg-positive), and duration of lamivudine treatment (mean, 3.8 years). At week 96 of treatment, 89.4% of patients in the TDF group and 86.3% in the FTC/TDF group had levels of HBV DNA <69 IU/mL (P = .43). HBeAg loss and seroconversion did not differ between groups; only 1 patient (0.7%) in the FTC/TDF group lost hepatitis B surface antigen. Treatment was well tolerated; confirmed renal events (creatinine increase of ≥0.5 mg/dL [>44 umol/L], creatinine clearance <50 mL/min, or level of PO4 <2 mg/dL [<0.65 mmol/L]) were generally mild and infrequent (<1%). Small reductions (<2%) in mean bone mineral density of hip and spine were detected by dual-energy x-ray absorptiometry in both groups. No TDF resistance developed through 96 weeks of treatment.
Conclusions: TDF alone is safe and effective for treatment of patients with lamivudine-resistant, chronic HBV infection.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2017
1 exp Hepatitis B/dt, th [Drug Therapy, Therapy] 8517
2 exp Lamivudine/ 5752
3 exp Tenofovir/ 2791
4 adefovir.mp. 2031
5 entecavir.mp. 1533
6 telbivudine.mp. 524
7 2 or 3 or 4 or 5 or 6 9837
8 1 and 7 4043
9 limit 8 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 174

Hepatitis B Antivirals

Goal(s):

- Approve treatment supported by medical evidence and consensus guidelines
- Cover preferred products when feasible for covered diagnosis

Length of Authorization:

Up to 12 months; quantity limited to a 30-day supply per dispensing.

Requires PA:

- All Hepatitis B antivirals

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Pediatric Age Restrictions:

- lamivudine (Epivir HBV) – 2-17 years
- adefovir dipivoxil (Hepsera) – 12 years and up
- entecavir (Baraclude) – 2 years and up
- telbivudine (Tyzeka) –16 years and up
- tenofovir disoproxil fumarate (Viread) – 12 years and up
- tenofovir alafenamide (Vemlidy) – safety and effectiveness not established in pediatrics

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the request for an antiviral for the treatment of HIV/AIDS?	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
4. Is the request for treatment of chronic Hepatitis B?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this a continuation of current therapy previously approved by the FFS program (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin."***	**Yes:** Go to Renewal Criteria	**No:** Go to #6
6. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	**Yes:** Document intolerance or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30-day supply.	**No:** Go to #7
7. Will the prescriber consider a change to a preferred product?	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve requested treatment for 6 months with monthly quantity limit of 30-day supply

Renewal Criteria	
1. Is the patient adherent with the requested treatment (see refill history)?	**Yes:** Go to #2
2. Is HBV DNA undetectable (below 10 IU/mL by real time PCR) or the patient has evidence of cirrhosis? Note: Antiviral treatment is indicated irrespective of HBV DNA level in patients with cirrhosis to prevent reactivation.	**Yes:** Approve for up to 1 year with monthly quantity limit of 30-day supply