Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: March 2014
PDL Classes: Hepatitis B Antivirals

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:
- Preferred Agents: LAMIVUDINE, TENOFOVIR DISOPROXIL FUMARATE
- Non-Preferred Agents: ADEFOVIR DIPIVOXIL, ENTECAVIR, TELBIVUDINE

Previous Conclusions and Recommendation:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- 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.

PA Criteria: Prior authorization criteria are currently in place for all hepatitis B antivirals with criteria to cover only covered diagnoses and for medically appropriate conditions (Appendix 1).

Conclusions and Recommendations:
- No further review or research needed at this time
- Update PA criteria to specify HBV undetectable levels and include a caveat for patients with decompensated cirrhosis (Appendix 1).
- Update pediatric age restriction of entecavir on PA criteria (Appendix 1).

Methods:
A Medline OVID search was conducted with the following search terms: lamivudine, tenofovir**,** adefovir, entecavir, telbivudine, hepatitis B virus. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week one 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
Zhao et al performed a systematic review and meta-analysis to establish the comparative efficacy of tenofovir versus adefovir for the treatment of hepatitis B. Six studies (n=910) were included in the analysis. The primary endpoint was viral suppression at 48 weeks (HBV-DNA level < 400 copies/mL). ALT normalization and antigen seroconversion were secondary endpoints. After 48 weeks of treatment, the tenofovir cohort had significantly higher HBV-DNA suppression than the adefovir group (RR=2.59; 95% CI 1.01 to 6.67). No difference was found between treatments in ALT normalization rates (RR=1.15; 95% CI 0.96 to 1.37). The difference of HBeAg seroconversion rates at week 48 between

the two group was similar (RR = 1.19; 95%CI 0.74 to 1.91). Individual trial quality was measured for adequate sequence generation, allocation concealment, how incomplete outcome data was addressed, and if free of selective reporting or other bias. Three trials were rated as high quality that adequately addressed all methodological quality concerns. The other three studies were rated as low quality with only the measures addressed incomplete outcome data and free of selective reporting sufficiently answered. All three reported endpoints were graded as low quality recommendations due to overall trial quality.[1]

Su et al conducted a systematic review and meta-analysis to compare the efficacy of telbivudine and entecavir in patients with hepatitis B. Primary outcomes included proportion of patients with undetectable HBV-DNA, HBV antigen loss or seroconversion. Secondary outcomes included percent ALT normalization, drug resistance and adverse outcomes. Thirteen trials (n=3925) were included in the analysis. Treatment duration ranged between four and 72 weeks. At 72 weeks, there was no statistical difference between telbivudine and entecavir in viral undetectability (RR 0.95; 95% CI 0.80 to 1.12). All time points between four weeks to 72 weeks (eight, 12, 24, 36, 48, 52, and 60 weeks) were also nonsignificant for viral nondetect rates for treatment. At weeks four, eight, 60 and 72, there was also no significant difference between the two treatments in antigen seroconversion; however at weeks 12, 24, 48 and 52, there was a significantly higher rate of seroconversion in the telbivudine group than the entecavir group (RR 2.10, 95% CI 1.36 to 3.24; RR 1.71, 95% CI 1.29 to 2.28; RR 1.86, 95% CI 1.36 to 2.54; and RR 1.87, 95% CI 1.21 to 2.90). There was no difference in rates of ALT normalization at any time point between treatment groups. Drug resistance was higher in the telbivudine cohort than the entecavir group at 72 weeks (RR=3.76; 95% CI 1.28 to 11.01). No serious adverse events were reported for either treatment; the most common side effects reported were flu-like symptoms and GI issues (diarrhea, nausea, vomiting). Creatinine kinase levels were significantly higher for the telbivudine group (RR=5.58; 95% CI 2.22 to 13.98). Individual trial quality was measured for adequate sequence generation, allocation concealment, how incomplete outcome data was addressed, and if free of selective reporting or other bias. The thirteen trials were given a grade of unclear for combined methodological quality matrices.[2]

Shi et al performed a meta-analysis evaluating nucleotide and nucleoside analogues in patients with hepatitis B and acute-on-chronic liver failure (ACLF). The primary outcome was three month mortality; HBV-DNA inhibition and ACLF reactivation were secondary endpoints. Five studies were included. Three were retrospective observational studies, and two were prospective randomized controlled trials. Only the end-point of three month mortality measured a head-to-head comparison of nucleotide analogues. Lamivudine and entecavir were compared for mortality rates. Rates were similar between treatment groups (entecavir 36.4% vs. lamivudine 40.5%, RR=0.77; 95% CI 0.45 to 1.32). All nucleotide and nucleoside analogues included (tenofovir, lamivudine and entecavir) were more effective than control at reducing HBV-DNA (70.4% vs. 29%, RR=2.29; 95% CI 1.49 to 3.53) and preventing ACLF reactivation (1.8% vs.18.4%, RR= 0.11; 95% CI 0.03 to 0.43). Individual trial quality was not assessed. Data was taking from observation as well as experimental trials further calling into question the quality of evidence of the findings.[3]

Guidelines:

In 2012, the International Antiviral Society-USA Panel published updated guidelines regarding antiviral treatment for HIV patients. This guideline included recommendations for patients coinfected with hepatitis B virus and HIV. Recommendations were graded for strength of the organization's support; an A grade was defined as having strong support, a B moderate support, and a C grade as having limited support. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from at least one randomized controlled trials (RCT) published in a peer-reviewed journal were given the ranking Ia. Ib recommendations were from evidence from at least one RCT presented in abstract form at a scientific meeting. IIa and IIb recommendations were based on evidence from nonrandomized clinical trials, cohort, or case-control studies either published in journals or presented at a scientific meeting respectively. III recommendations were based on the panel's analysis of the accumulated evidence.[4]

- The ART regimen for HIV- and HBV coinfected persons should include tenofovir and emtricitabine (or lamivudine) as the NRTI background (AIIa).

- In patients with reduced renal function, tenofovir should be avoided, or if treatment for hepatitis B virus (HBV) coinfection is needed, dosing should be adjusted according to the prescribing information (AIIa).

The Consensus guidelines for management of hepatitis B from the Canadian Association for the Study of the Liver were updated in 2012. Recommendations are based on benefit versus risk classification and the quality of evidence to support. In class I recommendations, the benefit of the intervention far outweighs any risk. Class II recommendations are split further into IIa and IIb; for both the benefit outweighs the risk, but class IIa interventions are termed 'reasonable' while IIb interventions are only to be considered. Class III recommendations are classified as having no benefit or possibly harmful. Level A recommendations are derived from data from multiple clinical trials or meta-analyses. Level B recommendations are based on data from a single RCT or nonrandomized studies. Level C recommendations are based on consensus opinion of expert, case studies, or standard of care.[5]

- The consensus guideline committee has recommended that PEG IFN remain one of the first-line treatments for chronic hepatitis B (Class IIa, Level A).
- Tenofovir or entecavir is first-line therapy for treatment-naïve HBV patients because they are the most potent agents available with no (tenofovir) or very low (entecavir) rates of antiviral resistance (Class I, Level A).
- Tenofovir is first-line therapy for lamivudine-resistant HBV. Entecavir should not be used in this setting due to the risk of development of entecavir resistance (Class I, Level A).
- The treatment of choice for lamivudine-resistant HBV infection is tenofovir (Class 2, Level A).
- If a patient requires treatment for HIV alone or for both HIV and HBV, include tenofovir plus either emtricitabine or lamivudine with an appropriate third anti-HIV drug (Class I, Level B).
- The withdrawal of an HBV-active antiviral drug could result in worsening of the HBV infection; it should be avoided if possible, but if done, HBV DNA and ALT need to be carefully monitored (Class I, Level B).
- If tenofovir is stopped and an alternate anti-HBV agent is used, then an appropriate anti-HIV agent should be substituted (Class 1, Level B).
- The recommended first-line treatment during pregnancy is tenofovir (FDA category B), telbivudine should be used if contraindications to tenofovir therapy to lower viral loads and if treatment is not expected to be prolonged postpartum (Class 2, Level B).

In 2012, The United Kingdom's National Institute for Clinical Excellence (NICE) updated its guideline recommendations for management of hepatitis B virus in children, adolescents, and adults.[6] The Guideline Development Group (GDG) for NICE made recommendations based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the supporting evidence. The guideline used 'must' or 'must not' only if there was a legal duty to apply the recommendation or if the consequences of not following the recommendation could be extremely serious or potentially life threatening. The words 'offer', 'refer' or 'advise' were employed when confident that an intervention will do more good than harm, and be cost-effective. The GDG used 'consider' when confident that an intervention will do more good than harm for most patients, and be cost-effective, but other options may be similarly cost-effective.

- Peginterferon alfa-2a (48 weeks) is recommended as first line treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications.
- Entecavir or tenofovir are recommended as second line treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
- Telbivudine is not recommended for the treatment of chronic hepatitis B.
- Do not offer adefovir dipivoxil for treatment of chronic hepatitis B.
- People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir, depending on previous antiviral exposure: Offer tenofovir disoproxil to people with a history of lamivudine resistance.

- If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil. In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.
- Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.
- Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.
- Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby.
- Offer prophylaxis therapy with entecavir or tenofovir if HBV DNA is greater than 2000 IU/ml and lamivude if HBV DNA is less than 2000 IU/ml.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 87 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, six relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Zheng et al compared telbivudine and entecavir for treatment of hepatitis B virus. Adult patients (n=131) were randomized to either 600 mg telbivudine or 0.5 mg entecavir once daily for 24 weeks. The primary endpoint was mean reduction in HBV-DNA serum levels at 24 weeks. Secondary end points included mean reduction from baseline in serum HBV-DNA concentration at week 12, the absence of serum HBV-DNA, absence of serum antigen (HBeAg), HBeAg seroconversion at week 24, the normalization of serum ALT at week 24, and occurrence of adverse events through week 24. The mean reduction in serum HBV-DNA was comparable between telbivudine and entecavir subjects at both weeks 24 (6.00 vs. 5.80 log10 copies) and 12 (4.99 vs. 4.69 log10 copies); for both, $p>0.05$. Rates of undetectable HBV-DNA levels were also similar between treatment groups. At 24 weeks, 67.7% of telbivudine and 57.6% of entecavir subjects were undetectable ($p=0.232$). At 12 weeks, 43.1% telbivudine and 34.8% entecavir patients were undetectable ($p=0.334$). Both absence of antigen and seroconversion rates were also nonsignificant between treatment groups at 24 weeks. Normalization of ALT levels was statistically similar as well at 24 weeks; 78.5% of telbivudine and 74.2% of entecavir subjects had ALT levels within normal limits ($p=0.57$). The most common adverse events were upper respiratory infections, diarrhea, cough, and fatigue. Adverse events were similar between groups with the exception of elevated creatinine; 12.3% of telbivudine patients vs. no entecavir patients had elevated creatinine from baseline at 24 weeks ($p=0.003$). This was a fair quality trial. It was an open label design which can introduce bias. In addition, randomization procedures were not explicitly described.[7]

Ryu et al studied the difference in efficacy of adding adefovir to lamivudine with entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. Patients (n=92) with a history of at least six months lamivudine treatment and current HBV-DNA levels greater than 10^5 log10 copies/mL were randomized to receive either lamivudine 100mg plus adefovir 10 mg or entecavir 1 mg for 12 months. The primary endpoint was the rate of undetectable patients at 12 months of treatment. Secondary endpoints included the reduction of HBV-DNA, the proportion of patients with ALT

normalization, HBeAg seroconversion, and nonresponse. At 12 months, 38.3% of lamivudine plus adefovir and 24.4% of entecavir had nondetectable levels of HBV-DNA (p=0.182). A greater mean reduction of HBV-DNA log 10 copies occurred in the lamivudine plus adefovir group than the entecavir group (3.80 vs. 2.72 log10 copies; p<0.001). More patients in the entecavir showed no response to treatment (defined as less than 2 log10 copies change from baseline after six months treatment) than the lamivudine/adefovir cohort (28.9% vs. 10.6%; p =0.036). Normalization of ALT levels and antigen seroconversion rates were similar between treatment groups (for both p>0.05). This was a poor quality study. It was an open label design which introduces bias. Treatment groups were not followed for the same amount of time and this was not addressed in the article; all endpoints were set at 12 months. In addition, methodology such as randomization was not described.[8]

Liaw et al conducted a study to compare entecavir with adefovir in patients with chronic hepatitis B with hepatic decompensation. Patients (n=191) with Child-Turcotte-Pugh score of at least seven were randomized to either entecavir 1 mg or adefovir 10 mg once daily for up to 96 weeks. The primary endpoint was the mean reduction in HBV-DNA at week 24. Secondary endpoints included percentage of patients to reach nondetectable serum levels at week 24, improvement in Child-Turcotte-Pugh score at week 48, and rates of adverse events by study end. Entecavir subjects showed a greater reduction in HBV-DNA than the adefovir group by week 24 (treatment difference -1.74 log10 copies; 95% CI -2.30 to -1.18). At week 24, significantly more entecavir patients were nondetectable than adefovir subjects (49% vs. 16%; p<0.0001); this trend continued at week 48 (57% vs. 20%; p<0.0001). Sixty-one percent of entecavir and 67% of adefovir patients showed some improvement or stabilization in Child-Pugh score. Adverse event rates were comparable between groups. Cumulative hepatocellular carcinoma rates were 12% for entecavir and 20% for adefovir. At week 24, mortality rates were 12% for both groups. It was an open label design which can introduce bias. In addition, randomization procedures were not explicitly described.[9]

Ha et al compared the efficacy of three regimens for hepatitis B therapy. Patients (n=91) were randomized to either adefovir 10 mg, adefovir 10 mg plus lamivudine 100 mg, or adefovir 10 mg plus entecavir 1 mg for at least 24 months. All subjects had prior treatment failure with lamivudine monotherapy and developed lamivudine resistance. The primary endpoint was mean reduction in HBV-DNA from baseline. Secondary outcomes included HBV-DNA undetectability (<60 IU/mL) and viral breakthrough. At 24 months, all three treatments showed a mean reduction in HBV-DNA: adefovir -3.78 IU/mL, adefovir plus lamivudine -4.92 IU/mL, and adefovir plus entecavir -5.58 IU/mL. This difference compared with adefovir monotherapy was statistically significant for both the adefovir plus lamivudine (p=0.026) and the adefovir plus entecavir (p=0.012) subjects. Difference in viral undetectability at 24 months, was nonsignificant for the all three treatment groups (adefovir 48.2%, lamivudine plus adefovir 76.7%, entecavir plus adefovir 87.5%). Subjects in the adefovir plus entecavir had not instances of viral breakthrough or mutations; 27.6% of adefovir patients and 13.3% adefovir plus lamivudine had viral breakthrough (for both compared with adefovir plus entecavir p<0.05). This was a low quality study with no description of blinding, randomization, or allocation concealment procedures.[10]

Lok et al evaluated the efficacy of entecavir monotherapy with entecavir plus tenofovir in patients with chronic hepatitis B. Subjects (n=379) were randomized to either entecavir 0.5 mg or entecavir 0.5 mg plus tenofovir 300 mg once daily for 100 weeks. The primary outcome was viral undetectability (<50 IU/mL) at 96 weeks. Both treatment groups had high rates of undetectability (83.2% patients on entecavir plus tenofovir and 76.4% on entecavir patients; p=0.088) with no statistical difference between groups. Adverse events were similar between treatment groups, although mean ALT levels normalized in more entecavir subjects than the dual therapy group (81.9% vs. 69%; p>0.05). This was a poor quality trial. It was open label design which can introduce bias, randomization methods were not described, and there were differences in group baseline characteristics.[11]

Yim et al compared the efficacy of entecavir with adefovir plus lamivudine to treat lamivudine resistant chronic hepatitis B. Subjects (n= 219) were randomized to either entecavir 0.5 mg or adefovir 10 mg plus lamivudine 100 mg for 24 months. The primary outcome was viral undetectability (<60 IU/mL) at 24 months. Rates of virologic breakthrough and

genotypic resistance were secondary endpoints. Patients in the dual treatment group were more likely to have nondetectable HBV-DNA levels at 24 months compared with entecavir subjects (56.7% vs. 40%; p= 0.025). Genotypic resistance (9.2% vs. 24.6%, P = 0.005) and combined viral breakthrough (2.0% vs. 17.6%, P < 0.001) were more frequent in the entecavir group. ALT normalization by treatment end was similar between groups (95.6% for the dual therapy group vs. 88.9% for the entecavir group; p=0.063). There were a couple serious adverse events tracked. Hepatocellular carcinoma developed in four patients from the adefovir plus lamivudine group and in one from entecavir group (p=0.368). Increased serum creatinine (>1.5 mg/dl) occurred in three patients from the combination group. No entecavir patients had elevated creatinine. This was a fair quality trial. It was an open label design which can introduce bias.[12]

References:

1. Zhao S-S, Tang L-H, Dai X-H, et al. Comparison of the efficacy of tenofovir and adefovir in the treatment of chronic hepatitis B: A Systematic Review. *Virology Journal*. 2011;8(1):111. doi:10.1186/1743-422X-8-111.

2. Su Q-M. Effects of telbivudine and entecavir for HBeAg-positive chronic hepatitis B: A meta-analysis. *World Journal of Gastroenterology*. 2012;18(43):6290. doi:10.3748/wjg.v18.i43.6290.

3. Yu S, Jianqin H, Wei W, et al. The efficacy and safety of nucleos(t)ide analogues in the treatment of HBV-related acute-on-chronic liver failure: a meta-analysis. *Ann Hepatol*. 2013;12(3):364-372.

4. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society–USA Panel. *JAMA*. 2012;308(4). doi:10.1001/jama.2012.7961.

5. Coffin CS, Fung SK, Ma MM, Canadian Association for the Study of the Liver. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. *Can J Gastroenterol*. 2012;26(12):917-938.

6. Sarri G, Westby M, Bermingham S, Hill-Cawthorne G, Thomas H, Guideline Development Group. Diagnosis and management of chronic hepatitis B in children, young people, and adults: summary of NICE guidance. *BMJ*. 2013;346:f3893.

7. Zheng M-H, Shi K-Q, Dai Z-J, Ye C, Chen Y-P. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. *Clinical Therapeutics*. 2010;32(4):649-658. doi:10.1016/j.clinthera.2010.04.001.

8. Ryu HJ, Lee JM, Ahn SH, et al. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *Journal of Medical Virology*. 2010;82(11):1835-1842. doi:10.1002/jmv.21898.

9. Liaw Y-F, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology*. 2011;54(1):91-100. doi:10.1002/hep.24361.

10. Ha M, Zhang G, Diao S, et al. Rescue Therapy for Lamivudine-resistant Chronic Hepatitis B: Adefovir Monotherapy, Adefovir Plus Lamivudine or Entecavir Combination Therapy. *Internal Medicine*. 2012;51(12):1509-1515. doi:10.2169/internalmedicine.51.7329.

11. Lok AS, Trinh H, Carosi G, et al. Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B. *Gastroenterology*. 2012;143(3):619-628.e1. doi:10.1053/j.gastro.2012.05.037.

12. Yim HJ, Seo YS, Yoon EL, et al. Adding adefovir vs. switching to entecavir for lamivudine-resistant chronic hepatitis B (ACE study): a 2-year follow-up randomized controlled trial. *Liver International*. 2013;33(2):244-254. doi:10.1111/liv.12036.

Appendix 1 PA criteria

Hepatitis B Antivirals

Goal(s):

- Cover hepatitis B agents according to OHP guidelines. Cover preferred products when feasible for covered diagnosis.
- Preferred products are selected based on evidence based reviews.

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.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Pediatric Age Restrictions:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Is the request for an antiviral for the treatment of HIV/AIDS?	Yes: Approve for up to 1 year	No: Go to #4
4. Is the request for treatment of Chronic Hepatitis B?	Yes: Go to #5	No: Pass to RPh, Deny for Appropriateness

Approval Criteria		
5. Is this a continuation of current therapy (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's supply.	No: Go to #7
7. Will the prescriber consider a change to a preferred product?	Yes: Inform provider of covered alternatives in class.	No: Approve requested treatment for 6 months with monthly quantity limit of 30 day's supply.

Renewal Criteria	
1. Is client compliant with requested treatment (see refill history)?	Yes: Go to 2.
2. Is HBV DNA undetectable (below 10-15 IU/ml by real time PCR) or the patient has decompensated cirrhosis)? Note: Antiviral treatment is indicated irrespective of HBV DNA level in patients with decompensated cirrhosis to prevent reactivation	Yes: Approve for up to 1 year with monthly quantity limit of 30 day's supply

P&T / DUR Action: *4/26/12*
Revision(s): *5/29/14 (MH)*
Initiated: *7/23/12*

Appendix 2: Abstracts of Randomized Control Trials

Zheng M-H, Shi K-Q, Dai Z-J, Ye C, Chen Y-P. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive chronic hepatitis B virus infection in adult Chinese patients. *Clinical Therapeutics*. 2010;32(4):649-658. doi:10.1016/j.clinthera.2010.04.001.

Background: Because drug-resistant strains of hepatitis B virus (HBV) have developed, and because serum HBV-DNA levels may rebound in patients who receive treatment with nucleoside/nucleotide analogues for up to 2 years, there remains a largely unmet clinical need for agents to induce potent virologic suppression in the initial stage of the disease course of HBV infection.

Objective: The aim of this work was to compare the early antiviral effectiveness of telbivudine and entecavir in the treatment of patients with hepatitis B e antigen (HBeAg)-positive HBV.

Methods: In this parallel-group, open-label trial, adult Chinese patients with previously untreated HBeAg-positive HBV (HBV-DNA concentration: ≥6 log10 copies/mL; alanine aminotransferase [ALT] level: ≥2 times the upper limit of normal) were randomized to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks. Blood samples were collected at the baseline and at 12 and 24 weeks after the treatment. The primary end point was the mean reduction from baseline in serum HBV-DNA concentration at week 24. Secondary end points included mean reduction from baseline in serum HBV-DNA concentration at week 12, the absence of serum HBV-DNA, absence of serum HBeAg, HBeAg seroconversion at week 24, the normalization of serum ALT at week 24, and occurrence of adverse events through week 24.

Results: A total of 131 patients were enrolled in the study: 91 men and 40 women, with a mean (SD) age of 32.5 (8.9) years. All patients were ethnic Han Chinese. The baseline demographic characteristics and serum HBV-DNA concentrations in the 2 treatment groups were well matched. Sixty-five patients were randomized to receive telbivudine and 66 to receive entecavir. The mean reductions from baseline in serum HBV-DNA were 4.99 and 4.69 log10 copies/mL at week 12, respectively, and 6.00 and 5.80 log10 copies/mL at week 24 (both time points, *P* = NS between groups). At week 12, HBV-DNA was undetectable in 43.1% (28/65) of the telbivudine group and 34.8% (23/66) of the entecavir group (*P* = NS); at week 24, it was undetectable in 67.7% (44/65) of the telbivudine group and 57.6% (38/66) of the entecavir group (*P* = NS). At week 12, HBeAg absence and seroconversion rates were significantly greater in the telbivudine group than the entecavir group (absence: 20.0% [13/65] vs 3.0% [2/66], respectively [*P* = 0.002]; seroconversion: 13.8% [9/65] vs 3.0% [2/66] [*P* = 0.030]). However, at week 24, HBeAg absence and seroconversion rates were comparable between the telbivudine and entecavir groups (absence: 36.9% [24/65] vs 28.8% [19/66] [*P* = NS]; seroconversion: 24.6% [16/65] vs 13.6% [9/66] [*P* = NS]). In addition, the normalization of ALT levels was observed in 78.5% (51/65) and 74.2% (49/66) of patients treated with telbivudine and entecavir, respectively, at week 24 (*P* = NS). The adverse events were upper respiratory tract infection (12.3% of telbivudine patients vs 9.1% of entecavir patients), fatigue (6.2% vs 7.6%), diarrhea (1.5% vs 3.0%), and coughing (0% vs 1.5%), most of which were mild to moderate. Elevated creatinine phosphokinase was noted in 8 telbivudine-treated patients (12.3%). There were no statistically significant differences in rates of adverse events between groups except for creatinine phosphokinase.

Conclusion: In this study of ethnic Han Chinese adults with previously untreated HBeAg-positive HBV infection, there were no statistically significant differences in effectiveness or tolerability between telbivudine 600 mg and entecavir 0.5 mg at the end of 24 weeks of treatment.

Ryu HJ, Lee JM, Ahn SH, et al. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *Journal of Medical Virology*. 2010;82(11):1835-1842. doi:10.1002/jmv.21898.

No study has reported on the comparative effect of adefovir (ADV) add-on lamivudine (LAM) versus switching to entecavir (ETV) in LAM-resistant patients with chronic hepatitis B. From October 2007 to September 2008, 92 consecutive LAM resistant patients were enrolled (47 LAMþADV and 45 ETV 1mg).All patients were followed for at least 12 months. The parameters assessed included normalization of ALT, HBeAg seroconversion, undetectable HBV DNA, reduction of HBV DNA, and predictors of virologic response. In the LAMþADV and ETV groups, the baseline DNA levels were 7.61 (5.19–9.49) and 7.10 (5.43–9.74) log10 copies/ml, respectively. At month 12, a virologic response occurred in 18/47 (38.3%) and 11/45 (24.4%; P¼0.182) patients; ALT normalization, in 39/41 (95.1%) and 36/40 (90.0%; P¼0.432); HBeAg seroconversion, in 5.1% and 2.4% (P¼0.606); and virologic breakthrough, in 2.1% and 11.1% (P¼0.107), respectively. The mean reduction from the baseline HBV DNA level was greater in the LAMþADV group at month 12 (3.80_1.12 vs. 2.72_1.32 log10 copies/ml; P<0.001). In the multivariate analysis, the independent parameters related to a virologic response at month 12 were baseline ALT (OR¼1.003, 95% CI¼1.000–1.006, P¼0.026) and baseline HBV DNA (OR¼0.495, 95% CI¼0.298– 0.823, P¼0.007). Compared with switching to ETV monotherapy, ADV add-on LAM therapy was more effective at reducing the viral load

inpatients with LAM resistance, and the baseline HBV DNA and ALT levels were independent predictors of the virologic response. However, ADV add-on therapy had limitations in patients with a higher baseline HBV DNA in LAM rescue therapy.

Liaw Y-F, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology*. 2011;54(1):91-100. doi:10.1002/hep.24361.

A randomized, open-label comparative study of entecavir versus adefovir therapy was performed in subjects with chronic hepatitis B who had hepatic decompensation (Child-Turcotte- Pugh score _7). Adult subjects were randomized and treated (n 5 191) with entecavir 1.0 mg or adefovir 10 mg daily for up to 96 weeks from the date of last subject randomization. Subjects were positive or negative for hepatitis B e antigen and experienced or naive for treatment with nucleos(t)ide analogues. The primary efficacy endpoint was the mean reduction in serum hepatitis B virus (HBV) DNA, as determined by polymerase chain reaction, at week 24, adjusted for baseline HBV DNA and lamivudine resistance status by linear regression analysis. Entecavir demonstrated superiority to adefovir for this endpoint (treatment difference 1.74 log10 copies/mL [95% confidence interval 22.30, 21.18]; P < 0.0001). The entecavir group showed a greater change from baseline in HBV DNA at all-time points through week 48 and a higher proportion of subjects who achieved HBV DNA < 300 copies/mL at weeks 24 (entecavir 49%; adefovir 16%; P < 0.0001) and 48 (entecavir 57%; adefovir 20%; P < 0.0001). Approximately two-thirds of subjects in both groups showed improvement/ stabilization in Child-Turcotte-Pugh status. Model for End-Stage Liver Disease score change at week 48 was 22.6 for entecavir and 21.7 for adefovir. Adverse event rates were comparable between groups. Cumulative hepatocellular carcinoma rates were 12% for entecavir and 20% for adefovir. Cumulative death rates were 23% for entecavir and 33% for adefovir. Week 24 mortality rates were 12% for both groups. Conclusion: Entecavir demonstrated superior virologic efficacy to adefovir in a population of patients with chronic hepatitis B who had hepatic decompensation. Biochemical and clinical benefits were also demonstrated. Entecavir was well tolerated, and early mortality rates were consistent with rates observed in similar populations treated with lamivudine.

Ha M, Zhang G, Diao S, et al. Rescue Therapy for Lamivudine-resistant Chronic Hepatitis B: Adefovir Monotherapy, Adefovir Plus Lamivudine or Entecavir Combination Therapy. *Internal Medicine*. 2012;51(12):1509-1515. doi:10.2169/internalmedicine.51.7329.

Objective We aimed to compare the cumulative efficacy and resistance of ADV monotherapy, ADV add-on LAM (ADV + LAM), ADV and ETV (ADV + ETV) combination therapy in LAM-resistant patients.

Methods Ninety-one adult CHB patients with LAM-resistance mutations (YMDD) were identified. Of these 91, 29 patients were treated with ADV monotherapy, 30 were treated with ADV + LAM and 32 were treated with ADV + ETV combination therapy, for at least 24 months.

Results The mean serum HBV-DNA decreases from baseline at 3, 6, 12, and 24 months were -3.23, -4.41, -5.32, and -5.58 log10IU/mL in the ADV + ETV combination therapy groups, respectively; the most significant among the three treatment groups (p<0.01). The rate of HBV-DNA PCR undetectability (<60 IU/mL) at 6 months in ADV + ETV combination therapy was 78.1%; also the most significant among the three treatment groups (p=0.024). Viral breakthrough and genotypic mutations were detected in 8 (27.6%) and 4 (13.3%) patients in the ADV monotherapy and ADV+LAM therapy groups, respectively; whereas no case of viral breakthrough and genotypic resistance was detected in the ADV+ETV combination therapy group after24 months (p<0.05).

Conclusion ADV + ETV combination therapy demonstrated faster and significantly greater suppression of HBV DNA compared with ADV add-on LAM combination therapy for patients with LAM-resistance mutations. ADV + ETV was superior to ADV + LAM in achieving initial virological response and long-term suppression activity against HBV. ADV + ETV combination therapy was the most effective to refrain from selecting HBV strains with cross-resistance to three NAs (LAM, ADV and ETV) for LAM-resistance patients.

Lok AS, Trinh H, Carosi G, et al. Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B. *Gastroenterology*. 2012;143(3):619-628.e1. doi:10.1053/j.gastro.2012.05.037.

BACKGROUND & AIMS: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent antiviral agents that might have additive or synergistic antiviral activity in treatment of patients with chronic hepatitis B (CHB). We compared the efficacy and safety of ETV monotherapy with those of a combination of ETV and TDF.

METHODS: We performed a randomized, open-label, multicenter, superiority study of 379 nucleos(t)ide-naïve patients with hepatitis B e antigen (HBeAg)-positive (n _264) or HBeAg-negative (n _ 115) CHB. Subjects were given ETV 0.5 mg (n _ 182) or a combination of ETV 0.5 mg and TDF 300 mg (n _ 197) for 100 weeks.

RESULTS: At week 96, comparable proportions of patients in each study arm achieved the primary end point of a level of hepatitis B virus (HBV) DNA _50 IU/mL (83.2% vs 76.4%; *P* _ .088). Among HBeAg-positive patients, a greater proportion given combination therapy achieved levels of HBV DNA _50 IU/mL than those given ETV alone (80.4% vs 69.8%; *P* _ .046). However, this difference was observed only in patients with baseline levels of HBV DNA _108 IU/mL (79% vs 62%) and not in those with baseline levels of HBV DNA _108 IU/mL (83% in both arms). Rates of HBeAg loss and HBeAg seroconversion were comparable between groups, whereas the rate of alanine aminotransferase normalization was greater in the ETV monotherapy group. No HBV variants associated with ETV or TDF resistance were detected. Safety profiles were consistent with previous reports of ETV or TDF monotherapy.

CONCLUSIONS: The antiviral efficacy of ETV monotherapy is comparable to that of ETV plus TDF in a mixed population of nucleos(t)ide-naïve patients with CHB (70% HBeAg positive). The combination therapy could provide an incremental benefit to HBeAg-positive patients with baseline levels of HBV DNA >108 IU/mL.

Yim HJ, Seo YS, Yoon EL, et al. Adding adefovir vs. switching to entecavir for lamivudine-resistant chronic hepatitis B (ACE study): a 2-year follow-up randomized controlled trial. *Liver International*. 2013;33(2):244-254. doi:10.1111/liv.12036.

Background: Management of lamivudine-resistant chronic hepatitis B (CHB) remains challenging, as inappropriate choice of treatment may cause multidrug resistance. Until now, randomized trials directly comparing adding adefovir and switching to entecavir monotherapy have not been reported.

Aims: This multicentre prospective randomized study was designed to compare the efficacy of these two strategies.

Methods: Two hundred and nineteen lamivudine-resistant CHB patients were randomized to either adefovir– lamivudine combination group or entecavir monotherapy group (n = 110 vs. 109), and followed up for 24 months.

Results: One hundred and eighty patients completed this study. At month 24, virological response rate [hepatitis B virus (HBV) DNA <60 IU/ml] was higher in the adefovir– lamivudine combination group compared with entecavir group (56.7% vs. 40%, P = 0.025), although biochemical and serological response rates were not significantly different. Genotypic resistance (9.2% vs. 24.6%, P = 0.005) and combined viral breakthrough (2.0% vs. 17.6%, P < 0.001) were more frequent in the entecavir group. However, by subgroup analysis, virological response rates were not significantly different between the two therapies in HBeAg-positive patients (44.9% vs. 35.7%, P = 0.268) or in patients with high baseline HBV DNA (_7 log IU/ml) (40.7% vs. 31.3%, P = 0.320) at month 24.

Conclusion: This study showed that adefovir–lamivudine combination provides significantly higher antiviral efficacy and the lower resistance rate compared with the entecavir monotherapy in the management of lamivudine- resistant CHB. However, it had limited efficacy in HBeAg-positive patients or in patients with high baseline HBV DNA.