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Hepatitis B Antivirals PA Criteria

Month/Year of Review: April 2012
Last Oregon Review: September 2010 (Provider Synergies)

The Oregon Health Resources Commission reviewed this class of agents for Chronic Hepatitis B (CHB) for addition to the Oregon PDL last September. The full source document can be found on the HRC website: http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/ps-2009-11-hep-b.pdf.

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harms/adverse events
3. Recommend including this class on the PDL and consider including entecavir (Baraclude) and tenefovir disoproxil fumarate (Viread)
4. Recommend establishing PA criteria for non-preferred products

Summary:

There are currently five oral nucleoside/nucleotide analogues (NA) available: lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. The long term clinical goals of antiviral therapy in CHB include reducing the development of cirrhosis, hepatocellular carcinoma, and death. There is moderate evidence suggesting that all of the NA have positive effects on one or more intermediate biomarkers associated with CHB including suppression of Hepatitis B Virus (HBV) DNA, normalization of serum alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg) loss or seroconversion, and hematologic response of improved necroinflammatory and fibrosis scores but no one treatment has shown to improve all biomarkers and there remains controversy over how these intermediate outcomes are related and if they predict clinical long term outcomes. The high-quality systematic review prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Minnesota Evidence-based Practice center concluded that observational studies suggest that male gender, coinfection with Hepatitis C, D, or HIV, increased HBV DNA, and cirrhosis were associated with an increased risk of hepatocellular carcinoma and death.[1] Although, there is limited direct evidence that any anti-HBV therapies have a beneficial impact on these clinical outcomes, there is growing evidence that prolonged and effective suppression of HBV DNA can decrease the risk of cirrhosis and hepatocellular carcinoma. This supports the current trend to use long term antiviral therapy. [2]

In addition to comparative efficacy evaluated in the Provider Synergies review,[3] randomized controlled trials demonstrated that tenofovir treatment resulted in statistically significant improvements in Hepatitis B viral suppression compared to adefovir in both HBeAg+ (76% vs. 13%, RR 5.8, 95% CI 3.35,9.73) and HBeAg- patients (93% vs. 63%, RR 1.5, 95% CI 1.28, 1.69).[4] It was also reviewed and recommended by the Canadian Agency for Drugs and

Technologies in Health (CADTH) as well as recommended in current treatment guidelines.[5] Guidelines from the Association for the Study of Liver (EASL), the American Association for the Study of Liver Disease (AASLD), the National Institute of Health (NIH), and a panel of US expert hepatologists have all published guidelines or consensus statements for the management of CHB. These all recommend peginterferon alfa, entecavir, and tenofovir as preferred first-line drugs for CHB based largely on efficacy and a lower risk of the development of drug resistance.[6–8] While these newer antiviral agents have the potential for prolonged effective viral suppression, more studies on the safety profiles and efficacy on long term use of these newer agents are needed. Future clinical trials should incorporate long term outcomes to align treatment with the surrogate markers and whether these markers reflect important clinical outcomes.

Other Considerations:

- 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.
- Combination therapy with NA has not has not proven to be superior to monotherapy in inducing a higher rate of sustained response.

Recommendations:

1. Establish prior authorization criteria for the non-preferred agents in this class to promote the use of the preferred and recommended products when feasible.
2. 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.

REFERENCES

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2. Lam Y-F, Yuen M-F, Seto W-K, Lai C-L. Current antiviral therapy of chronic hepatitis B: Efficacy and safety. *Current Hepatitis Reports*. 2011;10(4):235-243.

3. Provider Synergies, L.L.C. Hepatitis B Agents Review. 2009. http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/ps-2009-11-hep-b.pdf

4. 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. *Virol. J.* 2011;8:111.

5. Common Drug Review: TENOFOVIR DISOPROXIL FUMARATE. Final Recommendation and Reasons for Recommendation. Candadian Agency for Drugs and Technologies in Health (CADTH). Available at: http://www.cadth.ca/media/cdr/complete/cdr_complete_Viread-HBV_March-18-2009.pdf.

6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *Journal of Hepatology*. 2009;50(2):227-242.

7. Belongia E, Costa J, Gareen I, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med.* 2009;150:104-110.

8. Tong MJ, Hsu L, Chang PW, Blatt LM. Evaluation of current treatment recommendations for chronic hepatitis B: a 2011 update. *J. Gastroenterol. Hepatol.* 2011;26(5):829-835.

Suggested 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 1 year. Quantity limited to a 30 day supply per dispensing.

Pediatric age restrictions:

A. lamivudine (Epivir HBV)-2 years and up
B. adefovir dipivoxil (Hepsera)-12-17 years
C. entecavir (Baraclude)-16 years and up
D. telbivudine (Tyzeka)-safety and effectiveness not approved in pediatrics

Covered Alternatives that do not require a PA: See PDL list at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 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 treatment of Chronic Hepatitis B?	Yes: Go to #4	No: Pass to RPh, Deny for Appropriateness
4. 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 #5
5. 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 days supply.	No: Go to #6
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	Yes: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	No: Approve requested treatment for 6 months with monthly quantity limit of 30 days supply.

Renewal Criteria		
1. Is client compliant with requested treatment? (see refill history).	Yes: Go to 2.	No: Deny. Forward to RPH for provider consult.
2. Is HBV DNA undetectable?	Yes: Approve for up to 1 year with monthly quantity limit of 30 days supply	No: Deny. Forward to RPH for provider consult.