Clinical Policy: Hepatitis B Drugs- Entecavir (Baraclude) and Adefovir (Hepsera)

Reference Number: AZ.CP.PMN.03
Effective Date: 11.16.16
Last Review Date: 11.23
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Entecavir (Baraclude™) and adefovir (Hepsera®) are hepatitis B virus nucleoside analogue reverse transcriptase inhibitors.

FDA approved indications:

- Baraclude is indicated for the treatment of chronic hepatitis B virus infection in adults and children at least two years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
- Hepsera is indicated for the treatment of chronic hepatitis B in patients 12 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria.

It is the policy of Arizona Complete Health-Complete Care Plan and Care1st that Baraclude and Hepsera are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chronic Hepatitis B Infection (must meet all)**:**

1. Diagnosis of chronic Hepatitis B infection;
2. Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease specialist;
3. For entecavir member is ≥ 2 years age; for adefovir member is ≥ 12 years age.
4. Request is for adefovir (Hepsera), must meet all:
   a. Failure of one of the following, unless contraindicated or clinically significant adverse effects are experienced: Pegasys®, entecavir, or tenofovir;
   *Prior authorization may be required for Pegasys and entecavir (preferred formulation is tenofovir disoproxil fumarate);
   b. Hepsera is not prescribed concurrently with tenofovir;
   c. For member with lamivudine-resistant hepatitis B virus infection: lamivudine is being used in combination with adefovir;

5. Dose does not exceed the FDA-approved maximum recommended dose for the particular drug.

Approval duration: 12 months

B. Chronic Hepatitis B in patients co-infected with HIV (must meet all):

1. Diagnosis of chronic Hepatitis B infection and HIV;
2. Request is for entecavir (Baraclude);
3. Prescribed by or in consultation with a gastroenterologist, hepatologist or infectious disease specialist;
4. Unable to take tenofovir;
5. Taking antiretroviral treatment that includes either lamivudine or emtricitabine;
6. Dose does not exceed the FDA-approved recommended dose.

Approval duration: 12 months

C. Other diagnoses/indications

1. Refer to AHCCCS off label guideline if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

II. Continued Therapy

A. Chronic Hepatitis B Infection (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Centene Corporation or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Request is for adefovir (Hepsera): Hepsera is not prescribed concurrently with tenofovir;
4. If request is for a dose increase, new dose does not exceed FDA-approved maximum recommended dose for the particular drug.

Approval duration: 12 months

B. Chronic Hepatitis B in patients co-infected with HIV (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Centene Corporation or member has previously met initial approval criteria;
2. Request is for entecavir (Baraclude);
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed FDA-approved maximum recommended dose for the particular drug.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Centene Corporation and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to AHCCCS off label guideline if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the AHCCCS off-label use policy –or evidence of coverage documents

IV. Appendices/General Information

Appendix A: General Information

- A Patient co-infected with HIV should be evaluated by an HIV specialist to see if he/she needs to be treated with a HAART regimen that includes a component with activity against HBV (e.g. Viread®-tenofovir, Epivir®-lamivudine, or Emtriva®-emtricitabine).

Appendix B: Therapeutic Alternatives

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
Pegasys® (peginterferon alfa-2a)	180 mcg SC once weekly for 48 weeks	180 mcg/day
Tenofovir disoproxil fumarate (Viread)	300 mg PO QD For CrCl 30-49 ml/min: 300 mg PO Q 48 hours For CrCl 10-29 ml/min: 300 PO mg Q 72-96 hours For patients on hemodialysis: 300 mg PO Q 7 days or approximately 12 hours after dialysis	300 mg daily
Lamivudine (Epivir HBV)	Adults: 100 mg PO QD Pediatric patients age 2-17: 3 mg/kg, up to 100 mg QD Adjust dose in renal impairment	100 mg daily
Tenofovir alafenamide fumarate (Vemlidy)	25 mg PO QD	25 mg daily

Viread and Epivir HBV do not require Prior Authorization.
Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Entecavir (Baraclude)	Lamivudine-naïve patients: 0.5 mg PO QD CrCl 30-49 ml/min: 0.25mg PO QD CrCl 10-29 ml/min: 0.15 mg PO QD Hemodialysis: 0.05 mg PO following hemodialysis Lamivudine-experienced: 1 mg PO QD CrCl 30-49 ml/min: 0.5 mg PO QD CrCl 10-29 ml/min: 0.3 mg PO QD Hemodialysis: 0.1 mg PO QD	1 mg daily
Adefovir (Hepsera)	10 mg PO QD CrCl 30-49 ml/min: 10 mg PO Q 48h CrCl 10-29 ml/min: 10 mg PO Q 72h Hemodialysis: 10 mg PO Q 7 days following hemodialysis	10 mg daily

VI. Product Availability

Drug	Availability
Entecavir (Baraclude)	Tablets: 0.5 mg, 1 mg Oral solution: 0.05 mg/ml
Adefovir dipivoxil (Hepsera)	Tablets: 10 mg

VII. References

1. Baraclude Prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company; November 2019. Available at: https://packageinserts.bms.com/pi/pi_baraclude.pdf. Accessed September 28th, 2023.
2. Hepsera Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; December 2018. Available at: https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/hepsera/hepsera_pi.pdf Accessed September 28th, 2023.
3. Epivir HBV Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; September 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020564s37_020596s036lbl.pdf. Accessed September 28th, 2023.

4. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018; 67(4):1560-1599.
5. Sherman M, Yurdaydin C, Sollano J, et al. Entecavir is superior to continued lamuvidine for the treatment of lamuvidine-refractory HBeAg+ chronic hepatitis B: results of phase III study ETV-026 (abstr). *Hepatology* 2004;40:664A.
6. Lai CL, Rosmawati M, Lao J, et al. Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection. *Gastroenterology.* 2002;123:1831-1838.
7. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. March 2015. Available at: http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid=F33AA940563ABBB8DF1570D876EC494B?sequence=1. Accessed September 28th, 2023.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; Updated periodically. Accessed September 28th, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template Annual Review: - Simplified medical necessity criteria to require only diagnosis of Hepatitis B and prescription by an appropriate specialist. - Tyzeka discontinued 2016. Supply generally exhausted by December 2016. Removed Tyzeka from criteria.	06.14.17	11.17
Annual Review: No significant changes	08.29.18	
Annual Review: Added second indication for Baraclude of chronic Hepatitis B and coinfection with HIV.	08.01.19	7.2019
Annual Review; no significant changes; references reviewed and updated	08.01.20	07.2020
4Q 2020 annual review of Hepsera: no significant changes; references reviewed and updated.	08.08.20	11.20
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21
4Q 2021 annual review of Hepsera: no significant changes; references reviewed and updated.	11.2.21	11.21
Added criterion for patients with lamivudine-resistant HBV to use adefovir in combination with lamivudine per PI; references reviewed and updated.	02.09.23	02.23

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2023 annual review: no significant changes; clarified within criteria that preferred tenofovir formulation is tenofovir disoproxil fumarate; AZ.CP.PMN.53 retired, references updated to AHCCCS FFS Off-Label Guideline; references reviewed and updated.	09.28.23	11.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to

recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.