Clinical Policy: Obeticholic Acid (Ocaliva)

Reference Number: CP.PHAR.287
Effective Date: 11.16
Last Review Date: 08.21
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Obeticholic acid (Ocaliva®) is a farnesoid X receptor agonist.

FDA Approved Indication(s)

Ocaliva is indicated for the treatment of:

- Primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
- **[Pending]** Patients with fibrosis due to non-alcoholic steatohepatitis (NASH).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Ocaliva is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Primary Biliary Cholangitis (must meet all)**:**

1. Diagnosis of PBC;
2. Prescribed by or in consultation with a hepatologist or gastroenterologist;
3. Age ≥ 18 years;
4. Failure (as evidenced by sustained elevation in alkaline phosphatase level [ALP] ≥ 1.67 times the upper limit of normal) of ≥ 12 month trial of UDCA (ursodiol) at a dose of ≥ 13 mg/kg/day, unless contraindicated or clinically significant adverse effects are experienced;
5. Prescribed in combination with UDCA, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 10 mg (1 tablet) per day.

Approval duration: 6 months

B. Non-alcoholic Steatohepatitis [Preemptive Criteria]^ (must meet all)**:***

^Preemptive policy: This is a P&T approved policy and should only be used after this indication is FDA approved. Off-label requests prior to FDA approval should not be reviewed/approved using these criteria.
**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

1. Diagnosis of NASH;*
2. Fibrosis stage 2 or 3 as confirmed by one of the following (a or b):
   a. Liver biopsy:

b. Transient elastography or magnetic resonance elastography (MRE) and member is not a candidate for liver biopsy;
3. Prescribed by or in consultation with a hepatologist or gastroenterologist;
4. Age ≥ 18 years;*
5. A diagnosis of secondary steatohepatitis has been ruled out with absence of all of the following potential causes of liver fibrosis (a – j):
   a. Alcoholic liver disease;
   b. Viral hepatitis;
   c. PBC;
   d. Primary sclerosing cholangitis;
   e. Autoimmune hepatitis;
   f. Wilson's disease;
   g. Hemochromatosis (i.e., iron overload);
   h. Alpha-1 antitrypsin deficiency;
   i. HIV;
   j. Drug-induced liver injury (*see Appendix D for drug examples*);
6. Member does not have either of the following (a and b):
   a. Current or history of alcohol abuse;
   b. Scheduled liver transplant;
7. Documentation of adherence to lifestyle modification, including participation in diet and exercise program (*see Appendix D*), for at least the last 6 months;
8. If body mass index (BMI) ≥ 25, member has achieved and maintained ≥ 7% weight loss within the past 6 months;
9. Documentation of HbA1c ≤ 9.5% within the last 3 months;
10. Documentation of LDL < 190 mg/dL within the last 3 months;
11. Failure of a 6-month trial of pioglitazone or vitamin E at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated (*see Appendix B & D*);
12. Dose does not exceed 25 mg (1 tablet) per day.*

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Primary Biliary Cholangitis (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):
   a. Initial reauthorization: reduction in ALP level from pretreatment level;
   b. Subsequent reauthorization: continued reduction or maintenance of initial reduction in ALP level;

3. If request is for a dose increase, new dose does not exceed 10 mg (1 tablet) per day.

Approval duration: 12 months

B. Non-alcoholic Steatohepatitis [Preemptive Criteria]^ (must meet all)**:***

^Preemptive policy: This is a P&T approved policy and should only be used after this indication is FDA approved. Off-label requests prior to FDA approval should not be reviewed/approved using these criteria.
**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by one of the following (a or b):*
   a. Improvement in NASH fibrosis stage ≥ 1 with no worsening of NASH (i.e., no worsening of hepatocellular ballooning, lobular inflammation, or steatosis);
   b. No increase in NASH fibrosis stage and no worsening of NASH from baseline;
3. Documentation of adherence to lifestyle modification, including participation in diet and exercise program (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed 25 mg (1 tablet) per day.*

Approval duration: 6 months

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AASLD: American Association for the Study of Liver Diseases
ALP: alkaline phosphatase
FDA: Food and Drug Administration
ICER: Institute for Clinical and Economic Review
NASH: non-alcoholic steatohepatitis
PBC: primary biliary cholangitis
UDCA: ursodeoxycholic acid
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ursodiol (Urso®, Urso Forte®, Actigall®)	**PBC** 13-15 mg/kg/day PO in 2-4 divided doses	15 mg/kg/day
Vitamin E*	**NASH (without diabetes)** 800 IU/day PO	800 IU/day
pioglitazone (Actos®)*	**NASH (with or without diabetes)** 30 to 45 mg/day PO	45 mg/day

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.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event
  - Compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)
  - Complete biliary obstruction
- Boxed warning(s):
  - Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with Ocaliva treatment in PBC patients with either compensated or decompensated cirrhosis
  - Ocaliva is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension
  - Permanently discontinue Ocaliva in patients who develop laboratory or clinical evidence of hepatic decompensation; have compensated cirrhosis and develop evidence of portal hypertension; or experience clinically significant hepatic adverse reactions while on treatment

Appendix D: General Information

- Primary biliary cholangitis:
  - Ocaliva is approved under accelerated approval based on a reduction in ALP. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
  - According to the AASLD Primary Biliary Cirrhosis 2018 practice guidelines, UDCA dosed at 13-15 mg/kg/day orally is recommended for all patients with PBC who have abnormal liver enzyme values regardless of histological stage. Improvement in liver tests will be seen within a matter of a few weeks and 90% of the improvement usually occurs within 6-9 months. The eligibility criteria in the Ocaliva efficacy trial required enrolled patients to have a minimum 12 month history of taking UDCA.
  - In PBC patients with Child-Pugh Class B or C or decompensated cirrhosis, the recommended starting dose is 5 mg once weekly for these patients titrated to 10mg twice weekly (at least 3 days apart) based on response and tolerability.

- In the PBC clinical trial, response was defined as a composite of three criteria: ALP less than 1.67-times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%. The ULN for ALP was defined as 118 U/L for females and 124 U/L for males. The ULN for total bilirubin was defined as 1.1 mg/dL for females and 1.5 mg/dL for males.

- Non-alcoholic steatohepatitis:
  - Examples of medications causing microvesicular steatosis or secondary hepatosteatosis include mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids.
  - Lifestyle modification including diet, exercise and weight loss has been one of the standards of care for improving portal inflammation and fibrosis associated with NASH.
    - Per the 2018 AASLD NAFLD guidelines, the following are recommended:
      - Adherent caloric intake decrease by at least 30% or by approximately 500 to 1,000 kcal per day weight loss
      - Moderate-intensity exercise > 150 minutes per week or increase by more than 60 minutes/week
    - Per the 2016 EASL-EASD-EASO guidelines, the following are additionally recommended:
      - Exclusion of processed foods and beverages high in added fructose
      - Adherence to the Mediterranean diet
      - Aerobic and resistance training exercise
  - Pioglitazone has demonstrated statistically significant improvement in the nonalcoholic fatty liver disease activity score (NAS), which measures steatosis, inflammation, and ballooning, over placebo without worsening of fibrosis in clinical trials ranging from 6 months to 2 years. In two meta-analysis, pioglitazone use was associated with a statistically significant improved advanced fibrosis, fibrosis of any stage, and steatohepatitis resolution. The off-label use of pioglitazone in NASH patients with or without diabetes is supported by the 2018 AASLD guidelines, the 2012 World Gastroenterology Organization guidelines, and the European Association for the Study of the Liver guidelines.
  - In the 2-year PIVENS clinical trial, vitamin E compared to placebo achieved statistically significant higher rates of resolution of steatohepatitis (43% v. 19%, p = 0.001). Additionally vitamin E has also demonstrated statistically significant improvement in NAS in several clinical trials. Its off-label use in NASH patients without diabetes is supported by the 2018 AASLD guidelines, the 2012 World Gastroenterology Organization guidelines, and the European Association for the Study of the Liver guidelines.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PBC	5 mg PO QD titrated after 3 months to 10 mg PO QD based on efficacy and tolerability Dose adjustments required for Child-Pugh Class B/C or patients with prior decompensation event	10 mg/day

Indication	Dosing Regimen	Maximum Dose
NASH*	25 mg PO QD*	25 mg/day*

VI. Product Availability

Tablets: 5 mg, 10 mg, **[Pending]** 25 mg

VII. References

1. Ocaliva Prescribing Information. New York, NY: Intercept Pharmaceuticals, Inc.; May 2021. Available at https://ocaliva.com/. Accessed June 2, 2021.
2. Lindor, KD, Bowlus CL, Boyer J et al. Primary Biliary Cholangitis: 2018 Pracitice Guidance from the American Association for the Study of Liver Diseases (AASLD). Hepatology. 2018; 0(0): 1-26. Available at: https://www.aasld.org/sites/default/files/guideline_documents/PracticeGuidelines-PBC-November2018.pdf. Accessed May 7, 2020.
3. European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatology. 2017;67:145-72.
4. Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value. Institute for Clinical and Economic Review (ICER). March 19, 2020. Available at: https://icer-review.org/wp-content/uploads/2016/07/NECEPAC_OCA_NASH_Evidence_Report_FINAL.pdf. Accessed May 7, 2020.
5. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2019 Dec 14;394(10215):2184-2196. doi: 10.1016/S0140-6736(19)33041-7. Epub 2019 Dec 5.
6. Ratziu V, Sanyal AJ, Loomba R, et al. REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. Contemp Clin Trials. 2019 Sep;84:105803. doi: 10.1016/j.cct.2019.06.017. Epub 2019 Jun 29.
7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357.
8. LaBrecque D, Abbas Z, Anania F, et al. World Gastroenterology Organization Global guidelines: nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Clin Gastroenterol. 2014 Jul;48(6):467-73. doi: 10.1097/MCG.0000000000000116.
9. European Association for the Study of the Liver (EASL)1; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402. doi: 10.1016/j.jhep.2015.11.004. Epub 2016 Apr 7.
10. Musso G, Cassder M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med. 2017;177(5):633-640.

11. Boettcher E, Csako G, Pucino F, et al. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Ailment Pharmacol Ther. 2012; 35(1):66-75.

Reviews, Revisions, and Approvals	Date	Approval Date
3Q 2018 annual review: Policies combined for Commercial and Medicaid lines of business; added prescriber requirement; removed criteria confirming diagnosis; modified UDCA monotherapy trial duration to 12 months from 6 months based on Ocaliva package labeling and treatment guideline recommendations; references reviewed and updated	05.08.18	08.18
3Q 2019 annual review: no significant changes; modified gastrointestinal specialist to gastroenterologist; references reviewed and updated.	05.06.19	08.19
Added preemptive criteria for the pending FDA approval of NASH indication; added HIM line of business; for PBC, revised LFT elevations to ALP at least 1.67xULN.	03.10.20	05.20
3Q 2020 annual review: no significant changes; references reviewed and updated.	05.07.20	08.20
3Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	04.13.21	08.21
Disclaimer added for NASH preemptive criteria that they should only be used after this indication is FDA approved.	02.09.22	

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.