BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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OCALIVA™ (obeticholic acid) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Ocaliva (obeticholc acid) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Requesting provider is a physician specializing in the patient's diagnosis or is in consultation with a Hepatologist or Gastroenterologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of primary biliary cholangitis (PBC) without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension

  4. Ocaliva (obeticholic acid) use will be **ONE** of the following:
     a. With ursodeoxycholic acid (UDAC) in individuals who failed or had an inadequate response to appropriate doses of UDAC after 1-year use, defined as an ALP that is 1.67x upper limit of normal (UNL) and/or total bilirubin is > 1x UNL but < 2x UNL

     b. Without UDAC in those unable to tolerate or have an FDA-label contraindication to UDAC

  5. **TWO** of the following:
     a. Positive antimitochondrial antibodies (AMA) at a titer of 1:40 or more

     b. Presence of cholestasis with a history of increased ALP levels of at least 1.5x upper limit of normal (ULN) for more than 6 months

     c. Liver biopsy consistent with PBC that shows chronic non-suppurative cholangitis of the small and medium size bile ducts. A liver biopsy is typically not required.

  6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Child-Pugh classification

  7. There are **NO** FDA-label contraindications, such as:
     a. Decompensated cirrhosis (e.g., Child-Pugh Class B or C)
     b. Prior decompensation event
     c. Compensated cirrhosis with evidence or portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia
     d. Complete biliary obstruction

  8. There are no significant interacting drugs

  Initial approval duration: 3 months

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- **Criteria for continuation of coverage (renewal request):** Ocaliva (obeticholc acid) is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

  1. Individual continues to be seen by physician specializing in the patient's diagnosis or is in consultation with a Hepatologist or Gastroenterologist

  2. Individual's condition has responded while on therapy
     a. Response is defined as:
        i. Achieved and maintains ALP < 1.67x UNL or ALP decreased by at least 15% over baseline
        ii. Achieved and maintains total bilirubin is ≤ UNL

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use, such as:
     a. Contraindications as listed in the criteria for initial therapy section
     b. Significant adverse effect such as:
        i. Severe, persistent, intolerable pruritus that is intense or widespread, interfering with activities of daily living, or causes severe sleep disturbances or disconfort despite management strategies
        ii. Significant liver adverse reactions

  5. There are no significant interacting drugs

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Ocaliva (obeticholic acid) 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**. This indication was approved based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Treatment with Ocaliva (obeticholic acid) in patients with moderate and severe hepatic impairment should be initiated and monitored by a healthcare provider with experience managing PBC.

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Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile acid, derived from cholesterol, is found in small quantities in normal human bile. Oral administration of UDCA increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease. In addition to the replacement and displacement of toxic bile acids, other mechanisms of action include cytoprotection of the injured bile duct epithelial cells (cholangiocytes) against toxic effects of bile acids, inhibition of apotosis of hepatocytes, immunomodulatory effects, and stimulation of bile secretion by hepatocytes and cholangiocytes.

PBC (previously referred to as primary biliary cirrhosis) is an autoimmune disease that is characterized by progressive destruction of the small and medium sized intrahepatic biliary ducts. With ongoing inflammation and scarring of the bile ducts, bile cannot be carried from the liver to the intestine. There is progressive impairment of bile flow, increased hepatocellular bile concentration, and cellular injury. As a result, bile builds up in the liver causing cholestasis and jaundice (obstructive jaundice). Fibrosis and cirrhosis occur as the disease advances over a few years or in some a few decades. Most patients are asymptomatic at the time of their diagnosis, and it is often diagnosed based on elevated alkaline phosphatase (ALP). PBC was initially known as primary biliary cirrhosis but the name was changed due to cirrhosis being an advanced feature of the disease.

PBC is a relatively rare disease affecting 1 in 4,000 individuals and it is seen more commonly in females in a ratio of 9:1 with a peak incidence in the fifth decade of life. The diagnosis of PBC can be made by two of the following 3 American Association for the Study of Liver Diseases (AASLD) 2009 criteria: positive antimitochoindrial antibodies (AMA), presence of cholestasis with a history of increased ALP levels for more than 6 months, or liver biopsy consistent with PBC that shows chronic suppurative cholangitis of the small and medium size bile ducts. A liver biopsy is typically not required.

Bile acids are ligands of the nuclear receptor, farnesoid X receptor (FXR). The FXR is a member of the nuclear receptor superfamily that is highly expressed in liver, intestine, kidney, and adrenal glands. The most potent natural FXR ligand is chenodeoxycholic acid (CDCA, chenodiol), but other bile acids, cholic, lithocholic, and deoxycholic also activate FXR.

Obeticholic acid is an agonist for FXR. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. Recent studies show that FXR is the primary sensor of bile acids and is involved in every aspect of bile acid metabolism, including bile acid synthesis, transport, detoxification, and excretion in the liver and intestine. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing *de novo* synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.

In clinical trials, administration of Ocaliva (obeticholic acid) 10 mg once daily was also associated with an increase from baseline in concentrations of fibroblast growth factor (FGF)-19, an FXR-inducible enterokine involved in bile acid homeostasis. Concentrations of cholic acid and CDCA were reduced from baseline also. Fibroblast growth factors (FGFs) represent a large gene family of proteins involved in cell growth and differentiation, embryonic development, angiogenesis, and wound healing. FGF-19 is involved in controlling the enterohepatic bile acid/cholesterol system. FGF-19 also exerts important regulatory effects on glucose, protein, and lipid metabolism. The clinical relevance of these findings is unknown.

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Obeticholic acid is a modified bile acid with structural similarity to endogenous CDCA. Obeticholic acid is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of obeticholic acid are pharmacologically active and are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to obeticholic acid that can be reabsorbed or excreted in feces. A third obeticholic acid metabolite, 3-glucuronide, is formed but is considered to have minimal pharmacologic activity.

Definitions:

Diagnostic criteria for PBC: (from American Association for the Study of Liver Disease 2009)

Two of the following three criteria:

- Positive antimitochondrial antibodies (AMA)
- Presence of cholestasis with a history of increased ALP levels of at least 1.5x ULN for more than 6 months
- Liver biopsy consistent with PBC that shows chronic non-suppurative cholangitis of the small and medium size bile ducts. A liver biopsy is typically not required.

Child-Pugh Classification:

Child-Pugh Classification of severity of liver disease			
Child-Pugh Classification	Points		
A: Well compensated	5-6		
B: Significant functional compromise	7-9		
C: Decompensated	10-15		
Parameter/Factor	1 point each	2 points each	3 points each
Total Bilirubin: (mg/dL) or (µmol/L)	< 2 (or < 34)	2-3 (or 34-50)	> 3 or (> 50)
Albumin (g/dL) or (g/L)	>3.5 (or > 35)	2.8-3.5 (or 28-35)	< 2.8 (or < 28)
Prothrombin time			
Seconds over control	1-3	4-6	> 6
INR	< 1.7	1.71-2.3	> 2.3
Ascites	Absent	Slight/Mild	Moderate to severe
Encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

Decompensation events:

Appearance of ascites
Gastroesophageal variceal bleeding
New or worsening jaundice
Encephalopathy
Spontaneous bacterial peritonitis

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The appearance of ascites, variceal bleeding, jaundice, or encephalopathy, the major clinical manifestations of liver cirrhosis, marks the transition from the ***compensated*** phase into the ***decompensated*** phase of cirrhosis

Encephalopathy Grades:

Grade 0	• Minimal hepatic encephalopathy (also known as covert hepatic encephalopathy and previously known as subclinical hepatic encephalopathy) • Lack of detectable changes in personality or behavior • Minimal changes in memory, concentration, intellectual function, and coordination • Asterixis is absent
Grade 1	• Trivial lack of awareness • Shortened attention span • Impaired performance with addition or subtraction • Hypersomnia, insomnia, or inversion of sleep pattern • Euphoria or anxiety, depression, or irritability • Mild confusion • Slowing of ability to perform mental tasks
Grade 2	• Lethargy or apathy • Minimal disorientation for time and place • Inappropriate behavior • Impaired performance with subtraction • Slurred speech • Obvious asterixis • Drowsiness • Gross deficits in ability to perform mental tasks • Obvious personality changes
Grade 3	• Somnolence to semi-stupor, but responsive to verbal stimuli • Marked confusion • Gross disorientation • Unable to perform mental tasks • Amnesia • Occasional fits of rage • Incomprehensible speech
Grade 4	• Coma (unresponsive to verbal or noxious stimuli) • Coma with or without response to painful stimuli

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Resources:

Ocaliva (obeticholc acid) product information, revised by Intercept Pharmaceuticals, Inc. 05-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 30, 2021.

Ursodiol tab product information, revised by Par Pharmaceutical, Inc. 04-2018. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 31, 2021.

Urso 250 tab (ursodiol) and Urso Forte tab (ursodiol) product information, revised by Allergan, Inc 05-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 31, 2021.

Poupon R. Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis (primary biliary cirrhosis). In: UpToDate, Linder KD, Robson KM (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at Inc. http://uptodate.com. Accessed on July 31, 2021.

Poupon R. Overview of the management of primary biliary cholangitis. In: UpToDate, Linder KD, Robson KM (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on July 31, 2021.