

PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Ocaliva® (obeticholic acid tablets – Intercept Pharmaceuticals)

TAC APPROVAL DATE: 07/24/2019

OVERVIEW

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.¹ Ocaliva was approved for this indication under accelerated approval based on reduction in alkaline phosphatase (ALP). An improvement in survival or PBC-related symptoms has not been established. The prescribing information notes that continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Ocaliva is structurally similar to an endogenous bile acid, with the addition of an ethyl group in the 6-alpha position (6 α -ethyl-CDCA), which makes it a 100-fold more potent agonist at the Farnesoid X receptor (FXR), a nuclear receptor expressed in the liver and intestine.¹⁻² FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways.¹ Activation of FXR reduces the intracellular concentrations of bile acids in hepatocytes by suppressing *de novo* synthesis from cholesterol and by increased transport of bile acids out of the hepatocytes. In general, these mechanisms limit the amount of circulating bile acid, while promoting cholerisis, and therefore reduce hepatic exposure to bile acids.

Disease Overview

Primary biliary cholangitis (PBC) [also known as primary biliary cirrhosis] is a chronic, progressive, cholestatic liver disease in which autoimmune destruction of small and medium intrahepatic bile ducts leads to cholestasis.³⁻⁴ Cholestasis eventually progresses to advanced fibrosis, cirrhosis, and liver failure.³⁻⁵ The serologic hallmark of PBC is the finding of AMAs in the serum.³⁻⁴ AMA is a highly disease-specific autoantibody found in most, but not all patients with PBC (90% to 95%). In the 5% to 10% of patients in which AMA is absent or present only in low titer, nearly all will have PBC-specific antinuclear antibodies, including sp100 and gp210, which are present in over 30% of patients with PBC who are negative for AMA by indirect immunofluorescence. The biochemical hallmark of PBC is the finding of an elevated ALP level.⁵

Clinical Efficacy

POISE (PBC QCA International Study of Efficacy), a Phase III, randomized, double blind, published study, established the efficacy of Ocaliva in adult patients with PBC who either had an inadequate response to UDCA (93% of patients) or were unable to tolerate UDCA (7% of patients).² The primary efficacy endpoint was a composite of an ALP level < 1.67 times the upper limit of normal (ULN), a \geq 15% reduction in ALP, and a total bilirubin \leq ULN at Month 12. Significantly more patients receiving Ocaliva achieved the composite endpoint compared with placebo ($P < 0.0001$). An extension of the POISE study is ongoing, but through Year 3, Ocaliva therapy has resulted in a sustained reduction in ALP.^{2,6}

Guidelines

The American Association for the Study of Liver Disease (AASLD) guidelines for PBC (2018) state that the diagnosis of PBC can be confirmed when patients meet two of the following criteria: 1) there is cholestasis as evidenced by ALP elevation; 2) AMAs are present, or if AMA-negative, other PBC-specific autoantibodies, including sp100 or gp210, are present; 3) there is histologic evidence of

nonsuppurative destructive cholangitis and destruction of interlobular bile ducts. It is specifically noted that the diagnosis of PBC in a patient who is AMA-negative does not require a liver biopsy if other diagnostic criteria are met. In regards to the treatment of PBC, therapy with UDCA (available in the US as ursodiol [generic products], Urso 250[®] and Urso Forte[®]) at a dose of 13 to 15 mg/kg/day orally is the recommended treatment for patients with PBC who have abnormal liver enzyme values regardless of histologic stage.³ Following 12 months of UDCA therapy, the patient should be evaluated to determine if second-line therapy is appropriate. In patients who are determined to have an inadequate response to UDCA (estimated to be up to 40% of patients with PBC), treatment with Ocaliva should be considered. Fibrates could be considered as an off-label treatment alternative as well, but use of fibrates with Ocaliva is discouraged in patients with decompensated liver disease. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Diagnosis and Management of Patients with PBC (2017) make similar recommendations as the AASLD guidelines.⁷ Patients with PBC (both symptomatic and asymptomatic disease) should be treated with UDCA at 13 to 15 mg/kg/day on an ongoing basis. Biochemical response to UDCA should be evaluated at 1 year of therapy. Ocaliva is recommended for use in the patient population in which it has been studied (i.e., patients with elevated ALP/bilirubin who have had an inadequate response to UDCA or are intolerant to UDCA).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ocaliva. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocaliva as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocaliva to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ocaliva is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Primary Biliary Cholangitis (PBC) [also known as Primary Biliary Cirrhosis].** Approve Ocaliva for the duration noted if the patient meets one of the following conditions (A or B):
 - A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):
 - i. Patient is \geq 18 years of age; AND
 - ii. Ocaliva is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician; AND
 - iii. Patient has a diagnosis of primary biliary cholangitis (PBC) as defined by TWO of the following criteria (a, b, and/or c) according to the prescriber:
 - a) Alkaline phosphatase (ALP) elevated above the upper limit of normal as defined by normal laboratory reference values; AND/OR
 - b) Positive anti-mitochondrial antibodies (AMAs) or other PBC-specific auto-antibodies, including sp100 or gp210, if AMA is negative; AND/OR
 - c) Histologic evidence of primary biliary cholangitis (PBC) from a liver biopsy; AND

iv. Patient meets ONE of the following criteria (a or b):

- a) Patient has been receiving ursodiol therapy for \geq 1 year and has had an inadequate response according to the prescriber; OR
- b) According to the prescriber the patient is unable to tolerate ursodiol therapy.

Note: Examples of ursodiol therapy include ursodiol generic tablets and capsules, Urso 250[®], Ursodiol Forte[®] and Actigall[®].

- B)** Patients Currently Receiving Therapy. Approve for 1 year if the patient has responded to Ocaliva therapy as determined by the prescriber.

Note: Examples of a response to Ocaliva therapy are improved biochemical markers of primary biliary cholangitis (PBC) [e.g., alkaline phosphatase {ALP}, bilirubin, gamma-glutamyl transpeptidase {GGT}, aspartate aminotransferase {AST}, alanine aminotransferase {ALT} levels].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ocaliva has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Alcoholic Liver Disease.** There are no data available to support the use of Ocaliva in patients with alcoholic hepatitis. Ocaliva is not FDA-approved for this indication and current alcoholic liver disease guidelines from AASLD (2010) do not make recommendations regarding therapy with Ocaliva.^{1,8} Additional well-controlled studies are needed.
- 2. Nonalcoholic Fatty Liver Disease (NAFLD), including Nonalcoholic Fatty Liver (NAFL) or Nonalcoholic Steatohepatitis (NASH).** There are limited data available evaluating the efficacy of obeticholic acid in patients with NAFLD and NASH.⁹⁻¹³ A Phase III study is underway with an anticipated completion date in 2021.¹¹ Ocaliva is not FDA-approved for this indication and current NAFLD guidelines from AASLD (2018) recommend against the off-label use of obeticholic acid to treat NASH until additional safety and efficacy data become available.^{1,14} Additional well-controlled studies are needed.
- 3.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	06/01/2016
Annual Revision	No changes.	06/14/2017
Annual Revision	No changes.	07/11/2018
Annual Revision	<ul style="list-style-type: none">• Primary Biliary Cholangitis: Wording in reference to “according to the prescribing physician” was changed to “according to the prescriber”. For initial therapy approval, to confirm the diagnosis of primary biliary cholangitis, added that patients could be positive for anti-mitochondrial antibodies (AMAs) or other PBC-specific auto-antibodies including sp100 or gp210, if AMA is negative. Changed the approval duration for “Patients Currently Receiving Therapy” from 3 years to 1 year. Removed age requirement and specialist requirement from the criteria for “Patients Currently Receiving Therapy”.	07/24/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.