Medicines Management Programme

Managed Access Protocol – Obeticholic Acid (Ocaliva®▼) for the Treatment of Primary Biliary Cholangitis (PBC)

▼ This medicinal product is subject to additional monitoring. This will allow timely identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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AASLD	American Association for the Study of Liver Disease
ALP	Alkaline phosphatase
AMA	Anti-mitochondrial antibody
EASL	European Association for Study of the Liver
FXR	Farnesoid X receptor
HSE	Health Service Executive
HTH	High Tech Hub
MAP	Managed Access Protocol
MELD	Model for end-stage liver disease
MMP	Medicines Management Programme
NASH	Non-alcoholic steatohepatitis
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PDC-E2	Pyruvate dehydrogenase complex
PCRS	Primary Care Reimbursement Service
PSC	Primary sclerosing cholangitis
SmPC	Summary of product characteristics
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal

1. Obeticholic acid

Obeticholic acid (OCA) [Ocaliva®] is a selective and potent agonist for the farnesoid X receptor (FXR). FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing *de novo* synthesis from cholesterol, as well as by increasing transport of bile acids out of the hepatocytes.

From November 2022, two presentations of OCA are available on the High Tech Arrangement:

- Ocaliva® 5 mg film-coated tablets (30) ▼
- Ocaliva® 10 mg film-coated tablets (30) ▼

1.1 Licensed indication

OCA 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.[i]

1.2 Reimbursement

Reimbursement of OCA on the High Tech Arrangement is supported only for the licensed indication as outlined in section 1.1; reimbursement is not supported for any other indications.

Prescribers are required to apply for reimbursement approval on an individual patient basis. The *Obeticholic Acid for PBC Application Form* should be completed and sent by secure email to the Health Service Executive (HSE)-Medicines Management Programme (MMP) at mmp@hse.ie.

If a patient is recommended for reimbursement by the MMP, the high tech prescription for OCA should be generated on the High Tech Hub (HTH). High tech prescriptions that are not hub generated for OCA, will not be eligible for reimbursement by the HSE-Primary Care Reimbursement Service (PCRS).

Table 1 outlines the licensed dosing regimens of obeticholic acid (Ocaliva®) for the treatment of PBC.

[i] Please refer to the summary of product characteristics for Ocaliva® for full prescribing information.

Table 1: Licensed dosing regimens of obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis*

Patient population	Route	Starting dosage	Maximum dosage
Adults	Oral	5 mg once daily	10 mg once daily

mg: milligram

**In combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA*

After the first six months of treatment with OCA, for patients who have not achieved an adequate reduction in serum alkaline phosphatase (ALP) and/or total bilirubin and who are tolerating OCA, the dosage of OCA can be increased to a maximum of 10 mg once daily.

Please refer to the Summary of Product Characteristics (SmPC) for further information on posology including the management and dose adjustment for severe pruritus.

Reimbursement is supported up to the maximum licensed daily dosage of 10 mg daily, administered as one Ocaliva® 10 mg tablet daily, i.e. in line with the licensed dosage for the treatment of PBC as per SmPC. *See Section 3 for further details on Reimbursement Criteria - Continuation.*

1.3 Reimbursement price

The reimbursement prices of the presentations of OCA available on the High Tech Arrangement as of 1 November 2022 are outlined in table 2.

Table 2: Reimbursement price of the presentations of obeticholic acid (Ocaliva®) available on the High Tech Arrangement

Medicinal product (pack size)	Reimbursement	
	Code	Price
Ocaliva® 5 mg film-coated tablets (30)	89239	€2,892.33
Ocaliva® 10 mg film-coated tablets (30)	89240	€2,892.33

mg: milligram

A commercial-in-confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Ocaliva® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of OCA for the treatment of PBC under the High Tech Arrangement.

2.1 Prescribers

The prescribing of OCA under the High Tech Arrangement will be confined to consultant hepatologists and gastroenterologists registered with the Irish Medical Council, who have agreed to the terms of this Managed Access Protocol (MAP) and who have been approved by the HSE.

Applications for reimbursement approval will only be considered from these prescribers.

2.2 Patient age

Applications for reimbursement approval will only be considered for individuals aged ≥ 18 years at time of application.

2.3 Diagnosis

In line with American Association for the Study of Liver Disease (AASLD) and European Association for Study of the Liver (EASL) practice guidelines, clinicians are required to confirm a diagnosis of PBC for reimbursement approval. Clinicians must provide evidence of a documented diagnosis of PBC based on at least two of the three diagnostic factors outlined in sections 2.3.1, 2.3.2 and 2.3.3.

2.3.1 Serum ALP levels

For reimbursement approval, clinicians are required to confirm a history of sustained elevation (i.e. ≥ six months) of serum ALP levels above the upper limit of normal (ULN).

Clinicians are required to submit two serum ALP levels to support the diagnosis of PBC, and the date of the corresponding blood tests. The duration between the two blood tests should be ≥ six months.

2.3.2 AMA or PBC-specific antibodies

For reimbursement approval, clinicians are required to submit evidence to demonstrate serological positivity of anti-mitochondrial antibody (AMA) (i.e. positive titre of > 1:40).

In patients who are AMA negative or in low titre (< 1:80), clinicians should submit evidence to demonstrate presence of PBC-specific antibodies (anti-GP210 or anti-SP100) or antibodies against the major M2 components (pyruvate dehydrogenase complex [PDC-E2], 2-oxo-glutaric acid dehydrogenase complex).

2.3.3 Liver biopsy

For reimbursement approval, clinicians are required to submit a liver biopsy report consistent with PBC, i.e. histopathological evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts.

2.4 Patient clinical history

In line with the exclusion criteria from the POISE trial, and the SmPC of Ocaliva®, applications for reimbursement approval of OCA will not be considered in individuals with:

- decompensated cirrhosis (e.g. Child-Pugh Class B or C) or a prior decompensation event
- a history or a presence of other concomitant liver diseases
    - For example: hepatitis C virus infection, active hepatitis B infection, primary sclerosing cholangitis (PSC), alcoholic liver disease, definite autoimmune liver disease or overlap hepatitis, non-alcoholic steatohepatitis (NASH), Gilbert's Syndrome
- presence of clinical complications of PBC
    - For example: liver transplantation, model for end-stage liver disease (MELD) score ≥ 15, portal hypertension with complications
- a history of alcohol abuse or other substance misuse
- complete biliary obstruction
- a hypersensitivity to the active substance or any of the excipients of Ocaliva®.

2.5 Ursodeoxycholic acid

Clinicians will be required to provide details to demonstrate that the patient has had an inadequate response to UDCA, has not tolerated UDCA, or treatment with UDCA was contraindicated. The MMP may request evidence to validate treatment with UDCA.

2.5.1 Inadequate response to UDCA

Reimbursement will be supported for patients who have had an inadequate response to a trial of UDCA. A trial of UDCA is defined as a period of at least 12 months of treatment with UDCA, with at least three months at a dose of 13-15 mg/kg/day.

In order to demonstrate an inadequate response to UDCA treatment, clinicians must provide evidence of at least one of the following biochemical markers of PBC after the trial of UDCA:

- Serum ALP ≥ 1.67 x ULN
- Total bilirubin > ULN

2.5.2 Intolerant to UDCA

In cases where a patient did not tolerate UDCA and experienced a clinically significant adverse reaction which led to discontinuation of treatment prior to completion of a trial (as defined in 2.5.1), information in relation to the duration of treatment, dosage and the adverse reaction experienced must be provided.

2.5.3 Contraindication to UDCA

For patients in whom treatment with UDCA is contraindicated, details of the contraindication, including supporting evidence, must be provided at time of application for reimbursement approval.

2.6 Baseline serum ALP levels and total bilirubin

Clinicians are required to submit serum ALP levels and total bilirubin, taken within 30 days of the date of application, in order to establish baseline levels prior to commencement of treatment with OCA.

Please note that where the patient is currently in receipt of UDCA and classified as an inadequate responder, the baseline serum ALP levels and total bilirubin may be the same as those provided to demonstrate an inadequate response to UDCA, as per section 2.5.1.

3. Reimbursement criteria – Continuation

Patients with no improvement in biochemical markers of PBC (serum ALP and total bilirubin) after one year on the maximum tolerated licensed dosage of OCA, should be assessed based on the clinical course of PBC, and the potential benefits and risks of continued use of OCA. Prescribers should therefore monitor patient response and review the dosage of OCA in line with the SmPC, where indicated.[ii]

Patients not showing improvements as outlined above (i.e. no improvement in biochemical markers of PBC) would be considered as non-responders and consideration should be given to discontinuing treatment in such patients. Prescribers should only continue treatment if there is evidence of clinical benefit. Reimbursement of OCA under the High Tech Arrangement may no longer be supported in patients who are deemed non-responders.

After initiation of treatment with OCA, all patients should be monitored for progression of PBC disease, with laboratory and clinical assessment to determine whether OCA treatment should be

[ii] Please refer to the summary of product characteristics for Ocaliva® for full prescribing information.

discontinued. Patients at an increased risk of hepatic decompensation, including those with laboratory evidence of worsening liver function and/or progression to cirrhosis, should be monitored more closely.

Treatment with OCA should be permanently discontinued in patients with laboratory or clinical evidence of hepatic decompensation (e.g. ascites, jaundice, variceal bleeding, hepatic encephalopathy), including progression to Child-Pugh Class B or C, in line with the SmPC of OCA.

Therefore, following approval of a patient for reimbursement of OCA under the High Tech Arrangement, the prescribing clinician will be required to submit follow-up data by secure email to the MMP (mmp@hse.ie), including serum ALP and total bilirubin (and date of corresponding blood tests), as requested. The prescribing clinician should also indicate if they intend to continue or discontinue treatment with OCA.

Follow-up data may be requested by the MMP for audit purposes and provision of same is a condition of ongoing reimbursement.

4. Prescribing of Obeticholic Acid (Ocaliva® 5 mg/10 mg film-coated tablets)

Please refer to the SmPC for OCA for full prescribing information including monitoring and patient counselling requirements. Prescriptions must be generated through the HTH (details outlined separately) and only approved prescriber(s) will have access to prescribe OCA.

The following confirmations are required when prescribing obeticholic acid on the HTH:

- confirmation that obeticholic acid (Ocaliva®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE
- confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP
- confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

* Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.