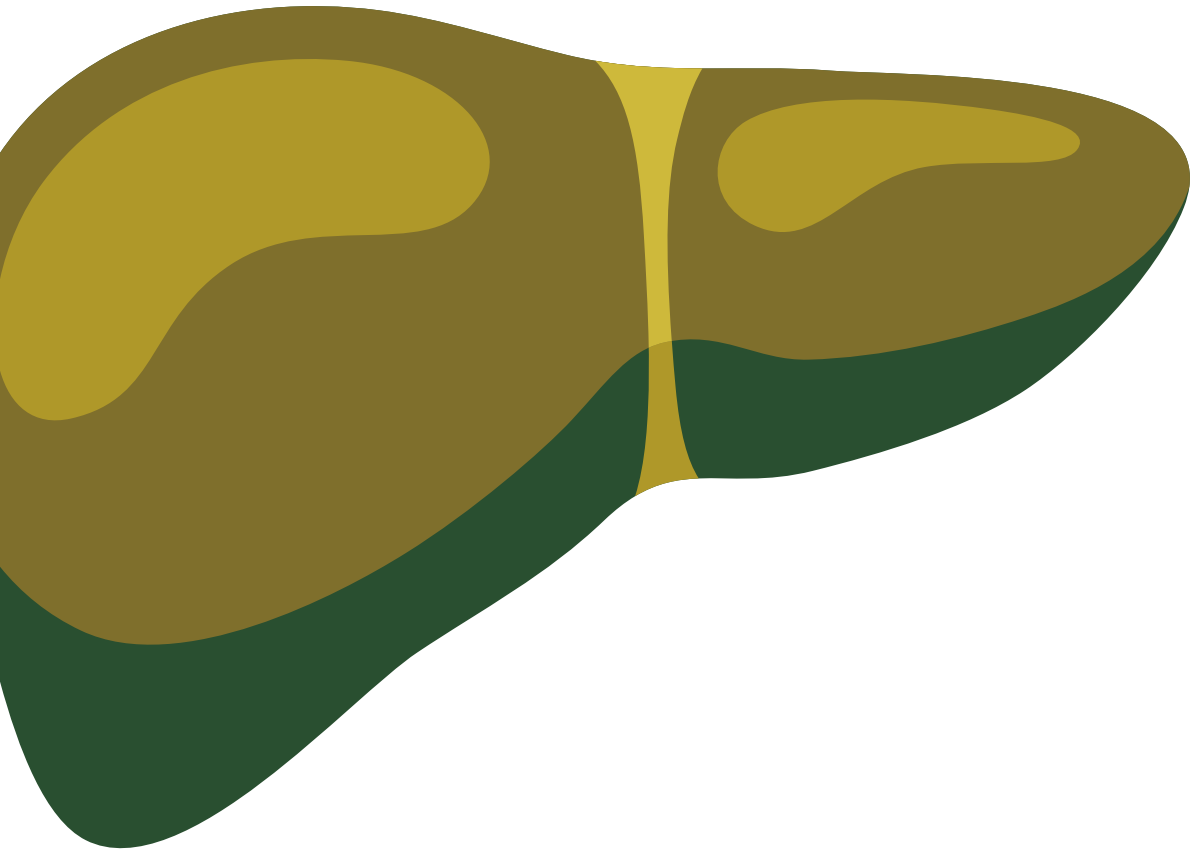
La Renon

UNLOCK *the* FLOW



Hebexr

Obeticholic Acid 5 mg and 10 mg Tablets

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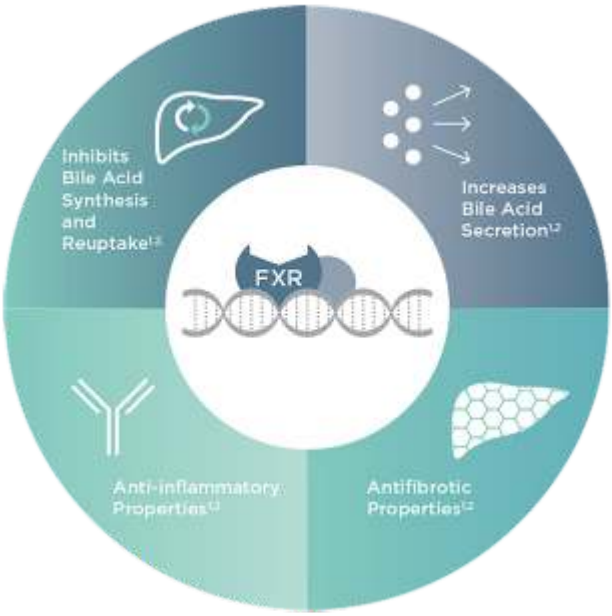
Introduction:

Primary biliary cholangitis (PBC) is a chronic liver disease in which the small bile duct in the liver become injured and inflamed and are eventually destroyed. When there are no bile ducts, bile builds up and causes liver damage. Formerly called primary biliary cirrhosis.

PHYSIOLOGICAL ROLES OF FXR WITHIN THE HUMAN DIGESTIVE TRACT

OBETICHOLIC ACID IS AN AGONIST FOR FXR, A NUCLEAR RECEPTOR EXPRESSED IN THE LIVER AND INTESTINE.



Reference:

1. Silveira MG, Lindor KD. Obeticholic acid and budesonide for the treatment of primary biliary cirrhosis. Expert Opin Pharmacother. 2014;15(3):365-372. doi:10.1517/14656566.2014.873404

2. Purohit T, Cappell MS. Primary biliary cirrhosis: pathophysiology, clinical presentation and therapy. World J Hepatol. 2015;7(7):926-941. doi:10.4254/wjh.v7.i7.926.

Clinical Evidence:

Long-term efficacy and safety of Obeticholic acid for patients with primary biliary Cholangitis: 3-year results of an international open-label extension study.

STUDY DESIGN	INDICATION	RESULT & OBSERVATION
The double-blind phase of POISE, 193 patients with primary biliary Cholangitis with inadequate response to or intolerance to Ursodeoxycholic acid were randomised to receive placebo, Obeticholic acid 5 to 10 mg, or Obeticholic acid 10 mg once daily for 12 months.	Patients with primary biliary Cholangitis with inadequate response to or intolerance to Ursodeoxycholic acid	Expression of CRP and mean ALP concentrations was significantly reduced from baseline to Obeticholic acid treatment, Total bilirubin concentrations were stabilized. Mean reductions from baseline for other liver enzymes were persistent.

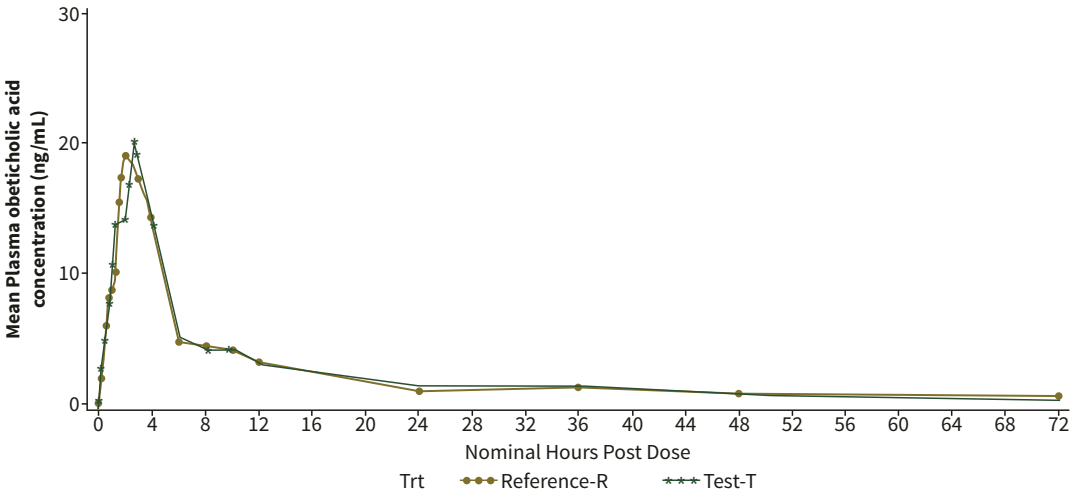
Reference: *http://dx.doi.org/10.1016/S2468-1253(19)30094-9*

Bioequivalence to OCALIVA®

PHARMACOKINETIC DATA FOR FED STUDY (BE-011-1119)

Parameters (Units)	Geometric Least Squares Means			90% Confidence Limits (%)	Power %	Intra Subject CV %
	Test product (T)	Reference product (R)	(T / R) %	(T vs. R)		
LOG C_{max} (ng/mL)	31.6352	32.7553	96.58	84.64 - 110.20	87.39	42.26
LOG AUC_{0-t} (ng.hr/mL)	149.4364	154.7008	96.60	89.64 - 104.09	99.92	23.27
LOG AUC_{0-inf} (ng.hr/mL)	185.2006	189.7128	97.62	91.67 - 103.96	100.00	19.51

Linear plot:

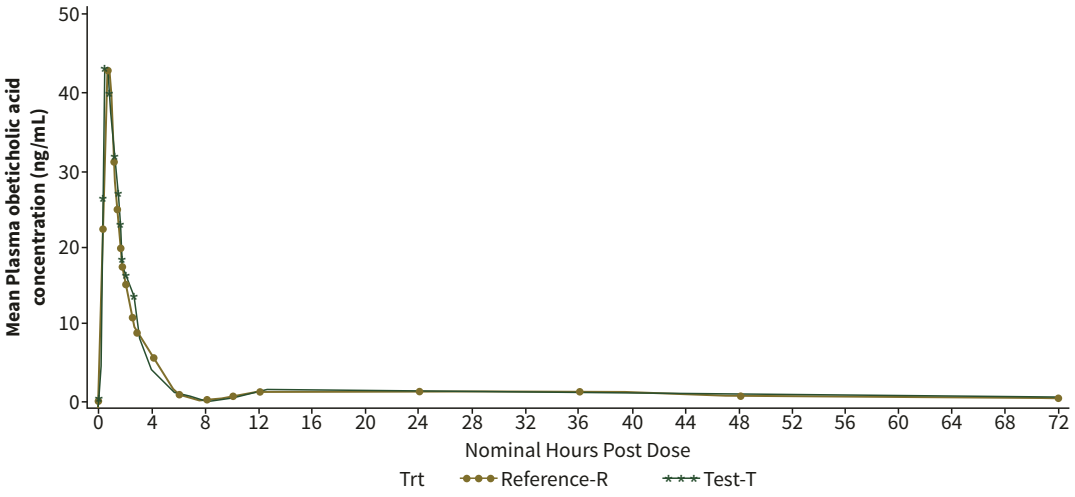


Comparison of in-vivo mean blood profile (N=53 human subjects) of Obeticholic acid Tablets 10mg with OCALIVA® (Obeticholic acid) Tablets 10mg used in pivotal bioequivalence study (fed condition).

PHARMACOKINETIC DATA FOR FASTING STUDY (BE-010-1119)

Parameters (Units)	Geometric Least Square Means and Ratio				90% Confidence Limits (%)	95% Upper Confidence Bound (Critical bound)	Power %	Intra Subject CV %
	Test product (T)	Reference product (R)	(T / R) %	% RSABE Ratio				
LOG AUC_{0-t} (ng.hr/mL)	147.7483	133.1712	110.95	—	103.55 - 118.87	—	99.97	22.68
LOG AUC_{0-inf} (ng.hr/mL)	188.2758	170.1906	110.63	—	101.87 - 120.13	—	99.70	29.41
LOG C_{max} (ng/mL)	61.1938	64.9303	—	96.55	—	-0.1221	95.77	45.15

Linear plot:



Comparison of in-vivo mean blood profile (N=47 human subjects) of Obeticholic acid Tablets 10mg with OCALIVA® (Obeticholic acid) Tablets 10 mg used in pivotal bioequivalence study (fasting condition).

Hebexr

Obeticholic Acid 5 mg and 10 mg Tablets

Description:

Hebexr is film coated tablet consisting of Obeticholic Acid 5 mg & 10 mg.

Indication:

Hebexr 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.

Mechanism of Action:

Hebexr (Obeticholic Acid)

A Potent agonist of the farnesoid X receptor → Acts by binding to the farnesoid X receptor (FXR) → Increases liver bile flow, suppressing its production → Decreasing hepatocytes exposure to excess level of bile with cholestasis

How OCA & UDCA Work:

Ursodeoxycholic Acid (UDCA)
Reduces elevated liver enzyme levels by facilitating bile flow through the liver and protecting liver cells.

When used together, OCA & UDCA have shown reductions in alkaline phosphatase beyond UDCA alone.

Obeticholic Acid
Inhibit bile acid synthesis and increase bile acid secretion to reduce hepatic exposure to bile acids.

Recommended Dosage:

Staging / Classification	**Non-cirrhotic patients or compensated cirrhotic patients with no or mild hepatic impairment (Child-Pugh Class A)**	**Cirrhotic patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) or Patients with a Prior Decompensation Event [a]**
Starting Obeticholic acid Dosage for first 3 months	5 mg once daily	5 mg once weekly
Obeticholic acid Dosage Titration after first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating Obeticholic acid[b]	10 mg once daily	5 mg twice weekly (at least 3 days apart) Titrate to 10 mg twice weekly (at least 3 days apart) based on response and tolerability
Maximum Obeticholic acid Dosage	10 mg once daily	10 mg twice weekly (at least 3 days apart)

[a] Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc.

[b] Prior to dosage adjustment, re-calculate the Child-Pugh classification

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