Seladelpar (LIVDELZI) in Primary Biliary Cholangitis
National Drug Mini-Monograph

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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; ALP, alkaline phosphatase; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial; ULN, upper limit of normal

FDA APPROVAL INFORMATION	
Description / MOA	Peroxisome proliferator-activated receptor (PPAR)-delta (δ) agonist. Inhibits bile acid synthesis. Seladelpar is the second PPAR agonist approved for primary biliary cholangitis (PBC), following elafibranor, which targets PPAR-alpha, -delta, and -gamma. Seladelpar is the fourth agent approved for PBC.
Indication Under Review[1]	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication was approved under accelerated approval based on a reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. *Limitations of Use.* Use of seladelpar is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).
Dosage Regimen	10 mg orally once daily with or without food
Dosage Forms Under Review	10-mg capsules
Pretreatment Evaluations	Clinical and laboratory liver assessments (ALT, AST, total bilirubin, alkaline phosphatase)
Monitoring During Therapy	Clinical and laboratory liver assessments as per routine patient care
Avoid in Patients With	Complete biliary obstruction Concomitant OAT3 inhibitors (e.g., probenecid, rifampicin) Concomitant strong CYP2C9 inhibitors (e.g., fluconazole, fluoxetine, ticlopidine)
Not Recommended in Patients With	Decompensated cirrhosis (see *Limitations of Use* above)

EFFICACY CONSIDERATIONS

RESPONSE Trial — **A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis[2] (2024)**

Design

12-month, multinational, double-blind, placebo-controlled RCT (randomized 2:1)

Primary End Point: Biochemical response, defined as ALP < 1.67 x ULN, ≥ 15% decrease in ALP from baseline, and normal total bilirubin at Month 12

Population

Diagnosis of PBC; inadequate response or unacceptable adverse effects with UDCA

Intervention

Seladelpar 10 mg daily

Comparator

Placebo

Background Therapy

UDCA in 93.8% of patients

Results

Efficacy Results

Outcome	Seladelpar	Placebo	RR (95% CI)	Diff (95% CI)	NNT (95% CI)	Q
Biochemical response at M12, n/N (%)	79/128 (61.7)	13/65 (20.0)	3.1 (1.9, 5.1)	41.7 (28.9, 54.6)	2.4 (1.8, 3.5)	$L^{\alpha\beta}$
ALP normalization at M12, n/N (%)	32/128 (25.0)	0/65 (0.0)	NC	25.0 (17.5, 32.5)	4.0 (3.1, 5.7)	$L^{\alpha\beta}$
CFB in Pruritus NRS to M6 (Moderate–Severe at BL) [n]*	–3.2 [49]	–1.7 [23]		–1.5 (–2.5, –0.5)	—	M^{β}
CFB in Pruritus NRS to M6 (Overall Population) [N]	–1.3 [128]	–0.4 [65]		–0.9 (–1.4, –0.5)	—	L^{β}

NRS, numerical rating scale

* In patients with baseline pruritus score of ≥ 4 (moderate–severe) on scale from 0 / No Itch to 10 / Worst Itch Imaginable. In chronic pruritus (≥ 6 weeks), the minimal clinically important difference (MCID) on a 0- to 10-point NRS is a 2- to 3-point decrease.[3]

[α] Downgraded for indirectness (surrogate for final clinical outcomes)

[β] Downgraded for imprecision (optimal information size not met; wide CI; and/or MCID not met)

Onset of Effect and Duration of an Adequate Trial

Based on mean CFB in ALP with seladelpar 5 mg and 10 mg:

- Onset is about 1 month.
- Duration of an adequate trial is 3 months.

Authors' Conclusions

At an optimal dose of 10 mg daily, seladelpar produced clinically significant anticholestatic effects and reduced signs of liver injury and pruritus in patients with PBC. There were no emergent safety concerns. The results suggest a potential role as second-line therapy to improve disease activity and symptoms.

ENHANCE Trial — **Seladelpar efficacy and safety at 3 months in patients with primary biliary cholangitis: ENHANCE, a phase 3, randomized, placebo-controlled study[4] (2023)**

Design

3-month results of a 12-month, multinational, dose- and placebo-controlled RCT (randomized 1:1:1) with 2-week run-in; stratified by ALP (< 350 or ≥ 350 U/L) and pruritus NRS (< vs ≥ 4).

Trial was terminated early because of unexpected histologic changes of the liver in a concurrent trial of seladelpar in metabolic dysfunction-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis / NASH). The histologic changes were subsequently deemed to be qualitatively not different from baseline and unrelated to seladelpar.

Primary Endpoint: Biochemical response, defined as ALP < 1.67 x ULN, ≥ 15% decrease in ALP from baseline, and total bilirubin ≤ ULN originally at Month 12, modified to Month 3.

Population

Adults 18–75 years old; diagnosis of PBC; ALP ≥ 1.67 x ULN and total bilirubin ≤ 2 x ULN; receiving a stable and recommended dose of UDCA (generally 13–15 mg/kg/d) for the previous 12 months unless intolerant. Patients with cirrhosis who did not have a history or current evidence of hepatic decompensation but met all other entry criteria were eligible. 94% (249/265) were on UDCA (mean dose 15.3 mg/kg/d) at baseline, and 100%, 15%, and 9% of patients had previously used UDCA, OCA, and fibrates, respectively.

Exclusions: AST or ALT > 3 x ULN; advanced PBC (coincident albumin < LLN and total bilirubin > 1 x ULN); creatine kinase > ULN; estimated glomerular filtration rate < 60 mL/min/1.73 m^2; international normalized ratio > ULN; PLT < 100 x 10^3/microL; clinically significant hepatic decompensation; other chronic liver disease. Use of OCA or fibrates within prior 30 days; colchicine, methotrexate, azathioprine, or systemic corticosteroids for > 2 weeks within previous 2 months; or simvastatin in previous 7 days.

Interventions

Seladelpar 5 mg orally once daily; could be up-titrated to 10 mg daily if primary end point not met at Month 6.

Seladelpar 10 mg orally once daily.

Patients on UDCA at baseline continued UDCA throughout the study.

Comparator

Placebo

Results

Efficacy Results

Outcome	SEL5	SEL10	Placebo	RR (95% CI) 10 mg vs PBO	AAE or Diff (95% CI), 10 mg vs PBO	NNT (95% CI) 10 mg vs PBO	Q
Biochemical response at M3, n/N (%)	32/56 (57.1)	43/55 (78.2)	7/56 (12.5)	6.3 (3.1, 12.7)	65.7 (51.7, 79.6)	3 (2, 4)	VL[α,β]
ALP normalization at M3, n/N (%)	3/56 (5.4)	15/55 (27.3)	0/56 (0.0)	Not calculable	27.3 (15.5, 39.0)	4 (3, 7)	VL[α,β]
CFB in Pruritus NRS to M3 (Moderate–Severe at BL) [n]*	–2.01 [17]	–3.14 [18]	–1.55 [18]	—	–1.59	—	L[α]

[α] Downgraded for potential overestimation of effect size due to early study termination and imprecision (optimal information size not met and/or wide CI)
[β] Downgraded for indirectness (surrogate for final clinical outcomes)

Authors' Conclusions

In patients with PBC, seladelpar 10 mg daily (optimal dose) provided clinically significant anticholestatic effects, improved signs of liver injury, and reduced pruritus without being associated with emergent safety concerns. The results suggested that seladelpar has potential for use as a second-line therapy for improving disease activity and symptoms.

Long-term Safety and Efficacy

Open-label, clinical trial extension: Two-year safety and efficacy results of seladelpar in patients with primary biliary cholangitis[5]

- This partially randomized, observational, safety and tolerability study involved patients who had completed the open-label phase 2 trial (n = 104) or the ENHANCE phase 3 trial (n = 2) and who continued receiving 2, 5, or 10 mg of seladelpar (n = 1, 18, or 87, respectively). Those with bilirubin > 2 mg/dL, or > 2 x ULN in ENHANCE, were excluded. Long-term efficacy was a secondary outcome.
- Only 53 of 106 enrolled patients completed 2 years in the study.
- At the beginning of the long-term study (Year 1), 63% to 66% met the composite endpoint of ALP < 1.67 x ULN, ≥ 15% decrease in ALP, and normal total bilirubin. After an additional year of treatment (Year 2), 79% of patients met the composite endpoint.
- 23%–26% had normalized ALP at Year 1, and 42% achieved normalization of ALP at Year 2.
- Therefore, during the additional year of treatment, an absolute, additional 13%–16% of patients achieved the composite endpoint and an additional 16%–19% of patients achieved normalization of ALP.

At Year 1 and Year 2, 54% and 43% of patients with elevated bilirubin at baseline achieved normalization of bilirubin, respectively, although the absolute changes were small, ranging from 0.3 to 1.5 mg/dL).

Other Studies

Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study[6]

Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis[7]

Evidence Gaps

Survival, mortality, hospitalization, readmission, liver-related outcomes (e.g., liver transplantation, prevention of liver decompensation)

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Avoid Use	Complete biliary obstruction OAT3 inhibitors Strong CYP2C9 inhibitors
Use Not Recommended	Decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)
Consider Discontinuing Therapy	Worsening of liver tests Progression to moderate or severe (Child-Pugh B or C) hepatic impairment
Interrupt Therapy	Worsening of liver tests or development of clinical hepatitis (e.g., jaundice, right upper quadrant pain, eosinophilia) Suspected biliary obstruction
Other Warnings / Precautions	Bone fractures Liver test abnormalities (observed at higher than recommended doses [50 mg and 200 mg daily]) Biliary obstruction
Top 5 AEs	Headache, abdominal pain, nausea, abdominal distension, dizziness
Laboratory Abnormalities	Decreased estimated glomerular filtration rate (eGFR) / elevations in serum creatinine – no associated clinical findings; values stabilized or returned towards baseline on continued seladelpar therapy
Drug Interactions	*OAT3 inhibitors (e.g., probenecid)*: AVOID concomitant use with seladepar *Strong CYP2C9 inhibitors*: AVOID concomitant use with seladepar *Rifampin*: Monitor for reduced seladelpar effects. *Bile acid sequestrants*: Monitor for reduced seladelpar effects. Administer seladelpar ≥ 4 hours before to ≥ 4 hours after taking a bile acid sequestrant, or at longest interval possible. *Dual moderate CYP2C9 and moderate-to-strong CYP3A4 inhibitors*: Monitor for seladelpar adverse effects. *CYP2C9 poor metabolizers using moderate-to-strong CYP3A4 inhibitors*: Monitor for seladelpar adverse effects. *BCRP inhibitors (e.g., cyclosporine)*: Monitor for seladelpar adverse effects.
Pregnancy	Insufficient human data. Reduction of fetal growth and pre-weaning survival of offspring with no malformations or adverse embryofetal survival were seen in animal studies. No clinical recommendations.
Lactation	Insufficient human data. Weigh benefits vs risks.
Geriatric Use	No overall differences in safety or effectiveness were seen between patients aged 65 to 75 years and younger adults. No dosage adjustment is necessary for patients ≥ 65 years of age.
Renal Impairment	No dosage adjustment for mild, moderate, or severe renal impairment. Not studied in patients with end-stage renal disease on dialysis.
Hepatic Impairment	*Mild (Child-Pugh A) Hepatic Impairment*: No dosage adjustment. *Moderate or severe (Child-Pugh B or C) hepatic impairment*: Consider discontinuing therapy.
Potential Safety Advantages vs Elafibranor	Lack of myalgia, myopathy, rhabdomyolysis at recommended dose of seladelpar. (At 5 and 20 times the recommended dose, patients with PBC experienced increases in liver transaminases, muscle pain, and/or increases in creatine phosphokinase (CPK). These adverse events resolved with discontinuation of seladelpar.) Effects on pruritus varied depending on the effect measure used.[8] Using the WI-NRS score, seladelpar significantly reduced itch, whereas elafibranor did not. Based on the 5-D itch scale score on quality-of-life measures, both agents improved pruritus. Using the itch domain of the PBC–40 questionnaire, elafibranor but not seladelpar showed significant improvement at Week 42. Neither PPAR agonist worsened pruritus as obeticholic acid (OCA) did.
Safety Evidence Gaps	Long-term safety; risk of decompensation in patients with cirrhosis

THERAPEUTIC OPTIONS				
Drug	**Formulary**	**CFU Place in Therapy**	**FDA Place in Therapy**	**2018 / 2021 AASLD Guideline Place in Therapy[9]**
PPAR-alpha / -delta Agonist				
Elafibranor	TBD	• Intolerance, inadequate response, or medical inadvisability to UDCA	• Treatment of PBC In combination with UDCA in inadequate responders to UDCA • Monotherapy in patients with UDCA intolerance • Not recommended in the presence of decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)	• Predates drug approval
PPAR-delta Agonist				
Seladelpar	TBD	• TBD	• Same as elafibranor	• Predates drug approval
Bile Acid				
Ursodiol (UDCA)	Yes (tab)†	• NA	• Treatment of PBC; no prerequisite therapies	• UDCA 13–15 mg/kg/d is first-line therapy. • Studies have inconsistently shown improved survival • Reduces need for liver transplant and improves transplant-free survival.
Farnesoid X Receptor Agonist Synthetic Bile Acid				
Obeticholic Acid (OCA)	No / CFU in PBC	• Contraindication or intolerance to UDCA or inadequate response after at least 12 months (stable dose for at least 3 months) of UDCA (13–15 mg/kg/day)	• Approved under accelerated approval based on reduction of ALP. Treatment of adults with PBC without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension either in combination with UDCA in inadequate responders to UDCA or as monotherapy in patients unable to tolerate UDCA. • Contraindicated in complete biliary obstruction, decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event, and compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) • Based on results of the confirmatory COBALT trial,[10] which showed that OCA was ineffective in preventing liver-related complications in patients with PBC, the FDA did not grant full approval of OCA for PBC.[11] OCA remains on the U.S. market as of 11/12/2024. It is unclear whether the FDA will withdraw OCA in the US.	• Contraindicated in advanced cirrhosis (defined as cirrhosis with current or prior evidence of liver decompensation, such as encephalopathy or coagulopathy, or evidence of portal hypertension (e.g., ascites, gastroesophageal varices, or persistent thrombocytopenia) • Recommends careful monitoring of *any* patients with cirrhosis who are on OCA
PPAR-alpha Agonist – Fibrates				
Fenofibrate‡	No (cap) Yes (tab)	• NA	• Off-label for PBC • Approved for treatment of hypertriglyceridemia, primary	• Fibrates can be considered off-label alternatives in inadequate responders to UDCA

Drug	Formulary	CFU Place in Therapy	FDA Place in Therapy	2018 / 2021 AASLD Guideline Place in Therapy[9]
			hypercholesterolemia, or mixed dyslipidemia	• Use is discouraged in decompensated liver disease
PPAR-alpha, -gamma, -delta Agonist – Fibrates				
Fenofibric Acid	No (cap EC, tab)	• NA	• See fenofibrate	• See fenofibrate

Sources: FDA Multi-discipline Review,**Error! Bookmark not defined.** UpToDate[12]
CFU, Criteria for Use

† Ursodiol capsules (e.g., RELTONE), on formulary, are not indicated for PBC.

‡ Use of fenofibrate in PBC is supported by a network meta-analysis of 5 studies: one observational study, two retrospective studies, and two meta-analyses. The NMA showed that fenofibrate + UDCA was better than UDCA and comparable to elafibranor + UDCA. [13]

POTENTIAL PLACE IN THERAPY	
2L therapy after UDCA	1. Seladelpar may be used as second-line, add-on therapy to UDCA in patients with PBC without decompensated cirrhosis who have an inadequate response to UDCA, or as monotherapy in patients who have intolerance to UDCA. An adequate trial of UDCA is considered to be ≥ 1 year at 13–15 mg/kg/d, with ≥ 3 months at a stable dosage.[14] 2. Seladelpar should be avoided in patients with complete biliary obstruction and patients taking concomitant OAT3 inhibitors or strong CYP2C9 inhibitors. 3. Seladelpar is higher priced than elafibranor but has potential safety advantages (lack of myopathy or rhabdomyolysis and maybe reduced itch).

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Contact person: Francine Goodman, PharmD, BCPS, National Program Manager, VA Pharmacy Benefits Management Services – Formulary Management (12PBM)

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