PDL DRUG REVIEW

Proprietary Name: Livdelzi®
Common Name: seladelpar lysine
PDL Category: Gastrointestinal Agents

Comparable Products	Preferred Drug List Status
Ocaliva (obeticholic acid)	Non-Preferred
Ursodiol	Preferred

Pharmacology/Usage: Seladelpar lysine, the active ingredient of Livdelzi®, is a peroxisome proliferator-activated receptor (PPAR)-delta agonist. However, the mechanism by which seladelpar exerts its therapeutic effects in patients with PBC is not well understood. Pharmacologic activity that is potentially relevant to therapeutic effects includes inhibition of bile acid synthesis through activation of PPAR-delta, which is a nuclear receptor expressed in most tissues, including the liver. Published studies demonstrate that PPAR-delta activation by seladelpar reduces bile acid synthesis through Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the main enzyme for the synthesis of bile acids from cholesterol.

Indication: For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have had an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is 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 trial(s).

Use of Livdelzi® is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

There is no pregnancy category for this medication; however, the risk summary indicates that there are insufficient data from human pregnancies exposed to Livdelzi® to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 10mg.

Recommended Dosage: The recommended dosage is 10mg PO QD, with or without food.

The recommended dosage in patients with mild, moderate, or severe renal impairment is the same as in patients with normal renal function. Patients with end-stage renal disease on dialysis have not been studied. Dosage adjustment is not recommended for patients with mild hepatic impairment. Use of Livdelzi® is not recommended in patients who have or develop decompensated cirrhosis. Monitor patients with cirrhosis for evidence of decompensation. Consider discontinuing Livdelzi® if the patient progresses to moderate or severe hepatic impairment.

Administer Livdelzi® at least 4 hours before or 4 hours after taking bile acid sequestrants, or at as great an interval as possible.

Drug Interactions: Avoid the co-administration of Livdelzi® with OAT3 inhibitors.

Avoid concomitant administration of Livdelzi® with strong CYP2C9 inhibitors.

The coadministration of Livdelzi® with rifampin may reduce the systemic exposure of seladelpar. Monitor the biochemical response (e.g., ALP and bilirubin) when patients start rifampin during treatment with Livdelzi®.

When Livdelzi® is concomitantly administered with drugs that are dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors, patients should be closely monitored for adverse effects.

Seladelpar is a CYP2C9 and CYP3A4 substrate. Concomitant use of a moderate to strong CYP3A4 inhibitor in patients who are CYP2C9 poor metabolizers may increase seladelpar exposure. Monitor CYP2C9 poor metabolizers who receive a concomitant moderate to strong CYP3A4 inhibitor more frequently for adverse reactions.

When Livdelzi® is concomitantly administered with drugs that inhibit BCRP, patients should be closely monitored for adverse effects.

Administer Livdelzi® at least 4 hours before or 4 hours after taking a bile acid sequestrant, or at as great an interval as possible.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Livdelzi®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (8%), abdominal pain (8%), nausea (5%), abdominal distension (6%), and dizziness (5%).

In Trial 1, fractures occurred in 4% of the Livdelzi® group as compared with no placebo-treated patients. The median time to fracture after receiving Livdelzi® was 295 days. Consider the risk of fractures in the care of patients treated with Livdelzi® and monitor bone health per current standards of care.

Livdelzi® has been associated with dose-related increases in serum transaminase greater than 3-times upper limit of normal (ULN) in PBC patients receiving 50mg once daily and 200mg once daily. Transaminase levels returned to pretreatment levels upon Livdelzi® discontinuation. Livedelzi® 10mg once daily did not show a similar pattern for increases in transaminase levels. Obtain baseline clinical and laboratory assessments at treatment initiation with Livdelzi® and monitor thereafter per routine patient management. Interrupt Livdelzi® treatment if the liver tests worsen, or the patient develops signs and symptoms consistent with clinical hepatitis. Consider permanent discontinuation if liver tests worsen after restarting Livdelzi®.

Avoid use of Livdelzi® in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt Livdelzi® and treat as clinically indicated.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Gilead Sciences, Inc.

Analysis: The efficacy of Livdelzi® was assessed in Trial 1, a 12-month, randomized, double-blind, placebo-controlled trial that included adult patients (N=193) with PBC with an inadequate response or intolerance to UDCA. Patients were included in the trial if their alkaline phosphatase (ALP) was greater than or equal to 1.67-times the upper limit of normal (ULN) and total bilirubin (TB) was less than or equal to 2-times the ULN.

Patients were randomized to receive Livdelzi® or placebo once daily for 12 months and both were administered in combination with UDCA in 181 patients (94%) during the trial or as a monotherapy in 12

patients (6%) who were unable to tolerate UDCA. The mean age of included patients was 57 years, while 95% were female, 88% were white, the mean baseline ALP concentration was 314 U/L (corresponding to 2.7-times ULN), and the mean baseline TB concentration was 0.8 mg/dl.

The primary endpoint was biochemical response at month 12, where biochemical response was defined as achieving ALP less than 1.67-times ULN, an ALP decrease of greater than or equal to 15% from baseline, and TB less than or equal to ULN. ALP normalization at month 12 was a key secondary endpoint. The ULN for ALP was defined as 116 U/L and for TB was defined as 1.1mg/dl.

The following table, adapted from the prescribing information, presents results of the study. Livdelzi® demonstrated greater improvement on biochemical response and ALP normalization at month 12 compared to placebo. Overall, 87% of patients had a baseline of TB concentration less than or equal to ULN. Thus, improvement in ALP was the main contributor to the biochemical response rate results at month 12.

	Livdelzi® (N=128)	Placebo (N=65)	Treatment difference, %
Biochemical Response Rate, n (%)	79 (62%)	13 (20%)	42%
NNT *calculated by CHC*	3		
Components of Biochemical Response			
ALP less than 1.67-times ULN, n (%)	84 (66%)	17 (26%)	39%
Decrease in ALP of at least 15%, n (%)	107 (84%)	21 (32%)	51%
TB less than or equal to ULN, n (%)	104 (81%)	50 (77%)	4%
ALP Normalization, n (%)	32 (25%)	0	25%

Biochemical response at month 3 comparing Livdelzi® as a monotherapy to placebo was assessed in a pooled analysis of a subset of patients from Trial 1 and another randomized, double-blind, placebo-controlled trial in a similar patient population. There was a trend of improvement on biochemical response at month 3 in the Livdelzi® monotherapy group as compared to placebo.

Regarding pruritus, a single-item patient-reported outcome (PRO), the pruritus Numerical Rating Scale (NRS), evaluated patients' daily worst itching intensity on an 11-point rating scale with scores ranging from 0 (no itching) to 10 (worst itching imaginable) in Trial 1. The pruritus NRS was administered daily in a 14-day run-in period prior to randomization through month 6.

The following table presents the results of the comparison between Livdelzi® and placebo on the key secondary endpoint assessing the change from baseline in pruritus score at month 6 in patients with baseline average pruritus scores greater than or equal to 4. The baseline average pruritus score for each patient was calculated by averaging the pruritus NRS scores administered in the run-in period and on day 1 before treatment initiation. The pruritus scores at month 6 for each patient were calculated by averaging the pruritus NRS scores within the last week in the month. Patients treated with Livdelzi® demonstrated greater improvement in pruritus compared with placebo.

	Livdelzi® (N=49)	Placebo (N=23)
Baseline average Pruritus Score, mean	6.1	6.6
Change from baseline in Pruritus Score at month 6		

	Livdelzi® (N=49)	Placebo (N=23)
Mean	-3.2	-1.7
Mean difference vs placebo	-1.5; p=0.0051	

Place in Therapy: Livdelzi® is a peroxisome proliferator-activated receptor (PPAR)-delta agonist indicated for the 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 is 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 trial(s). A limitation of use includes that use of Livdelzi® is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy). The efficacy of Livdelzi® was assessed in a randomized, double-blind, placebo-controlled study of 12 months duration that included adults with PBC with an inadequate response or intolerance to UDCA. The primary endpoint was biochemical response at month 12, and results suggested that Livdelzi® demonstrated greater improvement on biochemical response (and ALP normalization) at month 12 as compared to placebo. Per the full text by Hirschfield et al[2], the results of this primary endpoint were statistically significant in favor of Livdelzi® ($p < 0.001$). Head-to-head trials with other active comparators were not found.

Summary

There is no evidence at this time to support that Livdelzi® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Livdelzi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Livdelzi® [package insert]. Foster City, CA: Gilead Sciences; 2024.
[2] Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 trial of seladelpar in primary biliary cholangitis. *NEJM*. 2024; 390(9): 783-794.