▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
LIVDELZI® (seladelpar) capsules

1 NAME OF THE MEDICINE

Seladelpar.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 14.1 mg seladelpar lysine dihydrate equivalent to 10 mg seladelpar.

For the full list of excipients, see Section 6.1 *List of excipients*.

3 PHARMACEUTICAL FORM

Capsule.

Opaque, hard gelatin capsules, size 1, with light grey opaque body and a dark blue opaque cap, printed with “CBAY” on the cap and “10” on the body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LIVDELZI is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of LIVDELZI is 10 mg taken orally once daily with or without food.

Administration Instructions

LIVDELZI may be taken with or without food.

Missed Dose

If a dose of LIVDELZI is missed, the patient should take the subsequent dose at the next scheduled time point. A double dose should not be taken to make up for the missed dose.

Special populations

Paediatric population

The safety and efficacy of LIVDELZI in patients younger than 18 years of age have not been established.

Elderly

Limited data is available for elderly patients. No dose adjustment of LIVDELZI is required for patients aged 65 years or older.

Renal impairment

No dose adjustment of LIVDELZI is required in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate [eGFR] ≥ 15 mL/min). LIVDELZI has not been studied in patients with end stage renal disease (ESRD) on dialysis. No dose recommendation can be provided for this group.

Hepatic impairment

No dose adjustment of LIVDELZI is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of LIVDELZI in patients with decompensated cirrhosis have not been established. Use of LIVDELZI is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

Monitor patients with cirrhosis for evidence of decompensation. Consider discontinuing LIVDELZI if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C).

4.3 CONTRAINDICATIONS

LIVDELZI is contraindicated in patients with known hypersensitivity to seladelpar or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Effects on laboratory tests

Liver Test Abnormalities

LIVDELZI has been associated with dose-related increases in serum transaminase (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) levels greater than 3-times the upper limit of normal (ULN) in PBC patients receiving 50 mg once daily (5-times higher than the recommended dosage) and 200 mg (20-times higher than the recommended dosage) once daily. Transaminase levels returned to pretreatment levels upon LIVDELZI discontinuation. LIVDELZI 10 mg once daily did not show a similar pattern for increases in transaminase levels (see Section 4.9 *Overdose).*

Obtain baseline clinical and laboratory assessments at treatment initiation with LIVDELZI and monitor thereafter according to routine patient management. Interrupt LIVDELZI treatment if the liver tests (ALT, AST, total bilirubin [TB], and/or alkaline phosphatase [ALP]) worsen, or the patient develops signs

and symptoms consistent with liver dysfunction (e.g., jaundice, right upper quadrant pain, eosinophilia). Consider permanent discontinuation if liver tests worsen after restarting LIVDELZI.

Biliary Obstruction

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug Interaction Studies

In vitro studies

Based on *in vitro* studies, 10 mg seladelpar does not significantly affect the pharmacokinetics of concomitant drugs that are substrates of CYP enzymes (1A2, 2B6, 2C8, 2C19, 2D6), UGTs, P-gp, MATEs, OCT1, OCT2, OAT1, or OAT3. Seladelpar is a substrate of OATP1B1, OATP1B3, BCRP, P-gp, and OAT3 transporters *in vitro*. Seladelpar is not a substrate of MATE1, MATE2-K, OAT1, OCT1, or OCT2.

Effect of Other Drugs on Seladelpar

Drug interaction information for LIVDELZI with potential concomitant drugs is summarised in Table 1. The drug interactions described are based on the results of studies conducted with LIVDELZI or are potential drug interactions that may occur with LIVDELZI.

Table 1: Established and Other Potentially Significant Drug Interactions

Concomitant Drug or Class	Potential Effect on Exposure[a]	Clinical Comment
Probenecid (an OAT3 and OATP1B inhibitor)	↑ seladelpar	Avoid concomitant administration.
Strong CYP2C9 Inhibitors	↑ seladelpar	Monitor patients for adverse effects.
Dual Moderate CYP2C9 and Moderate to Strong CYP3A4 Inhibitors (e.g. fluconazole)	↑ seladelpar	Monitor patients for adverse effects.
Cyclosporine (an OATP1B, BCRP, and CYP3A4 inhibitor)	↑ seladelpar	Monitor patients for adverse effects.
Rifampicin (a strong CYP3A4 and moderate CYP2C9 inducer)	↓ seladelpar	Monitor patients for reduction in efficacy.

[a] ↑ = Increase, ↓ = Decrease.

Carbamazepine

Seladelpar $AUC_{0\text{-}inf}$ decreased by approximately 44% and C_{max} by 24% following administration of a single 10 mg seladelpar dose after 300 mg carbamazepine (a strong CYP3A and CYP2C9 inducer) twice daily for 8 days in healthy subjects. The carbamazepine dose was escalated from 100 mg twice daily for 3 days followed by 200 mg twice daily for 4 days to 300 mg twice daily.

Fluconazole

Seladelpar $AUC_{0\text{-}inf}$ increased by 2.4-fold and C_{max} by 1.4-fold following concomitant use of a single 10 mg seladelpar dose with 400 mg fluconazole (a moderate CYP2C9 and CYP3A4 inhibitor) in healthy subjects.

Cyclosporine

Seladelpar $AUC_{0\text{-}inf}$ increased by 2.1-fold and C_{max} by 2.9-fold following concomitant use of a single 10 mg seladelpar dose with 600 mg cyclosporine (an OATP1B1, OATP1B3, BCRP, and CYP3A inhibitor) in healthy subjects.

Probenecid

Seladelpar $AUC_{0\text{-}inf}$ increased by 2-fold and C_{max} by 4.69-fold following concomitant use of a single 10 mg seladelpar dose with 500 mg probenecid (an OAT3 and OATP1B1 inhibitor) in healthy subjects.

Quinidine

Seladelpar exposures were not significantly altered when a single dose of 600 mg quinidine (a P-gp inhibitor) was co-administered in healthy subjects.

Effect of Seladelpar on Other Drugs

Seladelpar has no clinically relevant effect on the pharmacokinetics of tolbutamide (a CYP2C9 substrate), midazolam (a CYP3A4 substrate), simvastatin (a CYP3A4 and OATP substrate), atorvastatin (a CYP3A4 and OATP substrate), and rosuvastatin (an OATP and BCRP substrate).

Bile acid binding resins

Bile acid binding resins such as colestyramine may reduce the absorption of other medicinal products administered concurrently. Patients should take seladelpar at least 4 hours before or 4 hours after taking a bile acid binding resin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies with seladelpar in humans have not been conducted.

Seladelpar had no effects on fertility or reproductive function in male and female rats at oral doses of up to 100 mg/kg/day (271-times the clinical exposure [based on AUC]).

Use in pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies of LIVDELZI in pregnant women. In animal reproduction studies, no malformations or effects on embryofetal survival occurred in pregnant rats or rabbits after seladelpar treatment at exposures of up to 195-times and 54-times the recommended dose based on AUC, respectively. In pregnant rabbits, oral administration of seladelpar at 40 mg/kg/day (exposures 54-times the clinical AUC) resulted in reduced gravid uterine weight and reduced fetal body weight. In pregnant rats, oral administration of seladelpar at doses of 0, 5, 20 or 100 mg/kg/day during gestation and lactation resulted in a dose dependent reduction in pup body

weights during the pre-weaning period at all dose levels, which was associated with slightly reduced pre-weaning survival at 100 mg/kg/day. Growth-related delays in developmental milestones were noted (eye opening and pinna unfolding at ≥ 5 mg/kg/day; hair growth and sexual maturity at 100 mg/kg/day). Growth reductions at 100 mg/kg/day continued into the post weaning maturation period and were considered adverse. The exposure at100 mg/kg/day was 271-times the clinical AUC at the recommended dose of 10 mg. The exposure at the NOAEL of 20 mg/kg/day was 34-times the clinical AUC. As a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy.

Use in lactation

It is not known whether seladelpar or its metabolites are secreted in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LIVDELZI and any potential adverse effects on the breastfed infant from LIVDELZI or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of LIVDELZI on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the RESPONSE trial, 193 patients were randomised (2:1) to receive either LIVDELZI 10 mg (n=128) or placebo (n=65) once daily for 12 months. During RESPONSE, LIVDELZI or placebo was administered in combination with UDCA in 94% of patients and as monotherapy in 6% of patients who were unable to tolerate UDCA. The overall treatment discontinuation rate due to adverse events was 3.1% in the LIVDELZI 10 mg arm and 6.2% in the placebo arm. A total of 118 patients completed 1 year of treatment with LIVDELZI 10 mg.

The frequencies of the adverse drug reactions provided in the table below are based on pooled data from two controlled clinical trials (RESPONSE and ENHANCE) in which 306 patients with PBC received 5 mg or 10 mg LIVDELZI once daily.

Frequencies are defined according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Table 2: Adverse drug reactions reported in clinical trials in patients treated with LIVDELZI

System Organ Class	Very Common (≥ 1/10)	Common[a] (≥ 1/100 to < 1/10)
Nervous System Disorders		Headache
Gastrointestinal Disorders	Abdominal pain[b]	Nausea Abdominal distension

[a] Frequency based on all patients receiving LIVDELZI in RESPONSE and ENHANCE.

[b] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

Based on the clinical trial experience, the most frequently reported adverse reactions were abdominal pain (11.1%), headache (7.2%), and nausea (6.5%). These adverse reactions were non-serious and did not lead to the discontinuation of LIVDELZI.

Laboratory Abnormalities

Serum Creatinine

Dose dependent increases in serum creatinine have been observed in LIVDELZI-treated patients. In RESPONSE, median increases of up to 6.6% were observed with the 10 mg dose compared with up to 2.2% in patients taking placebo. Increases were not progressive and returned towards baseline with ongoing LIVDELZI treatment. None of the patients required discontinuation of LIVDELZI and there were no clinical findings associated with the observed changes in serum creatinine.

Experience from Long-term Studies

In ASSURE, an open label study in patients with PBC (N=280) who received LIVDELZI, with a median duration of exposure of 54 weeks (min, max: 1 day to 124 weeks), the safety profile was similar to that in RESPONSE.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

PBC patients who received 5-times the recommended dosage or 20-times the recommended dosage of LIVDELZI experienced an increase in liver transaminases, muscle pain, and/or elevations in creatine phosphokinase, which resolved upon LIVDELZI discontinuation [see Warnings and Precautions for Use (5.1)]. There is no specific treatment for overdose with LIVDELZI. General supportive care of the patient is indicated, as appropriate. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because seladelpar is highly bound to plasma proteins, haemodialysis should not be considered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Seladelpar is a peroxisome proliferator-activated receptor (PPARδ) agonist, or delpar. PPARδ is a nuclear receptor expressed in the liver and other tissues. PPARδ activation reduces bile acid synthesis in the liver through Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol, and by decreasing cholesterol synthesis and absorption. These actions result in lower bile acid exposure in the liver and reduced circulating bile acid levels. Seladelpar also has positive effects on serum lipids and fibrosis in a CCl4 liver fibrosis mouse model.

Pharmacodynamics

In clinical studies, LIVDELZI treatment resulted in reduction of ALP, a biomarker of cholestasis. ALP reduction was observed within 1 week of treatment initiation, continued to decrease through Month 3, and was sustained through Month 24.

In RESPONSE, the median changes in serum 7α-hydroxy-4-cholesten-3-one (a bile acid synthesis intermediate) and total bile acids at Month 12 were -41.9% and -32.0%, respectively, after treatment with LIVDELZI, reflecting action leading to diminished cholestatic accumulation of total bile acids. LIVDELZI also increased mean serum FGF21 levels by 76.2% after 12 months of treatment; this increase is a known effect of PPARδ activation in hepatocytes that leads to decreased bile acid synthesis.

In RESPONSE, treatment with LIVDELZI led to mean changes of -44.9% and -31.6% in the pruritogenic cytokine IL-31 after 6 and 12 months of treatment in patients with moderate-to-severe pruritus, which was associated with improvements in pruritus severity.

Decreases in triglycerides, LDL-C, and total cholesterol were noted with LIVDELZI treatment.

Effects on Electrocardiogram

At a dose of 20-times the maximum recommended dose, LIVDELZI was not associated with clinically significant QT prolongation.

Clinical trials

The efficacy of LIVDELZI was evaluated in RESPONSE, a 52-week, randomized, double-blind, placebo-controlled trial. The trial included 193 adult patients with PBC with an inadequate response or intolerance to UDCA. Patients were included in the trial if their ALP was greater than or equal to 1.67-times the ULN and total bilirubin (TB) was less than or equal to 2-times the ULN. Patients were excluded from the trial if they had other chronic liver diseases, clinically important hepatic decompensation including portal hypertension with complications, or cirrhosis with complications (e.g., Model for End Stage Liver Disease [MELD] score of 12 or greater, known esophageal varices or history of variceal bleeds, history of hepatorenal syndrome).

Patients were randomized (2:1) to receive LIVDELZI 10 mg (N=128) or placebo (N=65) once daily for 12 months. LIVDELZI or placebo was administered in combination with UDCA in 181 (94%) patients during the trial, or as a monotherapy in 12 (6%) patients who were unable to tolerate UDCA.

The mean age of patients was 57 (Range: 28 to 75) years; 95% were female; 88% were White, 6% Asian, 2% Black or African American, and 3% American Indian or Alaska Native. Twenty-nine percent of the patients, 23% in the LIVDELZI 10 mg arm and 42% in the placebo arm, identified as Hispanic/Latino.

At baseline, 18 (14%) of the LIVDELZI-treated patients and 9 (14%) of the placebo-treated patients met at least one of the following cirrhosis criteria: Fibroscan > 16.9kPa; historical biopsy or radiological evidence suggestive of cirrhosis; platelet count < 140,000/µL with at least one additional laboratory finding including serum albumin < 3.5 g/dL, INR > 1.3, or TB > 1-time ULN; or clinical determination of cirrhosis by the investigator. All cirrhosis patients had Child-Pugh A status at baseline.

The mean baseline ALP concentration was 314 (Range: 161 to 786) units per liter (U/L), corresponding to 2.7-times ULN. The mean baseline TB concentration was 0.8 (Range: 0.3 to 1.9) mg/dL and was less than or equal to the ULN in 87% of the patients. Other mean baseline liver biochemistries were 48 (Range: 9 to 115) U/L for ALT, corresponding to 1.2-times the ULN; 40 (Range: 16 to 94) U/L for AST, corresponding to 1.2-times the ULN; and 288 (Range: 42 to 1088) U/L for gamma glutamyl transferase (GGT), corresponding to 1.7-times the ULN.

Baseline Demographics and Characteristics

The two treatment groups were generally balanced with respect to baseline, demographics and disease characteristics.

Table 3: Summary of Baseline Disease Characteristics and Laboratory Values in RESPONSE

	LIVDELZI (N = 128)	**Placebo (N = 65)**	**Total (N = 193)**
Baseline Disease Characteristics			
Duration of PBC (years)[a]			
Mean (SD)	8.2 (6.70)	8.6 (6.46)	8.3 (6.60)
Min, Max	0.4, 27.0	0.2, 33.0	0.2, 33.0
Subjects with Cirrhosis at Baseline (Child-Pugh Class CP-A)	18 (14.1)	9 (13.8)	27 (14.0)
Liver Stiffness by FibroScan (kPa), m			
Mean (SD)	9.8 (6.16)	8.7 (4.18)	9.5 (5.56)
Min, Max	3.1, 43.2	3.8, 23.0	3.1, 43.2
UDCA Intolerance[b,], n (%)			
Yes	8 (6.3)	4 (6.2)	12 (6.2)
No	120 (93.8)	61 (93.8)	(181) (93.8)
Prior Use of OCA and/or Fibrates, n (%)			
Yes	20 (15.6)	13 (20.0)	33 (17.1)

	LIVDELZI (N = 128)	Placebo (N = 65)	Total (N = 193)
No	108 (84.4)	52 (80.0)	160 (82.9)
Pruritus NRS for subjects with baseline Pruritus NRS ≥ 4, n	49	23	72
Mean (SD)	6.1 (1.4)	6.6 (1.4)	6.3 (1.4)
Min, max	4, 9	4, 9	4, 9
Baseline Laboratory Values			
ALP (U/L), n; (reference range: 37-116)			
Mean (SD)	314.6 (122.96)	313.8 (117.68)	314.3 (120.90)
Min, Max	182, 786	161, 698	161, 786
Total Bilirubin (mg/dL), n; (reference range: 0.1-1.10)			
Mean (SD)	0.769 (0.314)	0.737 (0.310)	0.758 (0.312)
Min, Max	0.31, 1.88	0.26, 1.95	0.26, 1.95
ALT (U/L), n; (reference range: 6-41)			
Mean (SD)	47.4 (23.47)	48.2 (22.83)	47.7 (23.20)
Min, Max	13, 109	9, 115	9, 115
AST (U/L), n; (reference range: 9-34)			
Mean (SD)	39.6 (16.14)	41.7 (16.03)	40.3 (16.09)
Min, Max	16, 94	16, 84	16, 94
Albumin (g/dL), n; (reference range: 3.50-5.50)			
Mean (SD)	4.2 (0.27)	4.1 (0.23)	4.1 (0.26)
Min, Max	3.0, 4.8	3.6, 4.6	3.0, 4.8

[a] Duration of PBC (time [in years] from diagnosis date to informed consent date) was defined (informed consent date – PBC diagnosis date +1)/365.2424

[b] UDCA intolerance was from UDCA usage at baseline.

In RESPONSE, the primary endpoint was a composite biochemical response at Month 12, where biochemical response was defined as achieving ALP less than 1.67-times the ULN, an ALP decrease of greater than or equal to 15% from baseline, and total bilirubin less than or equal to ULN. The ULN for ALP was defined as 116 U/L. The ULN for total bilirubin was defined as 1.1 mg/dL.

LIVDELZI demonstrated significantly greater improvement on biochemical response and ALP normalization at Month 12 compared to placebo. Seladelpar treatment led to a significantly higher percentage of subjects (61.76%) achieving the primary efficacy endpoint of composite biochemical response at Month 12 compared with placebo (20.0%) ($p < 0.0001$). Treatment outcomes of the RESPONSE trial are presented in Table 4.

Table 4: Efficacy Results of LIVDELZI With or Without UDCA in RESPONSE

	LIVDELDI 10 mg (N=128)	Placebo (N=65)	Treatment Difference % (95% CI)[d]
Biochemical Response Rate, n (%)[a,b] [95% CI]	79 (62) [53, 70]	13 (20) [10, 30]	42 (28, 53) p < 0.0001
Components of Biochemical Response			
ALP less than 1.67-times ULN, n (%)	84 (66)	17 (26)	39 (25, 52)
Decrease in ALP of at least 15%, n (%)	107 (84)	21 (32)	51 (37, 63)
Total bilirubin less than or equal to ULN[d], n (%)	104 (81)	50 (77)	4 (-7, 17)
ALP Normalization[c]			
ALP Normalization at Month 12, ≤1.0×ULN (%)[b,c] [95% CI]	32 (25) [18, 33]	0 (0) [0, 0]	25 (18, 33) p < 0.0001

Patients who discontinued treatment prior to Month 12 or who had missing data were considered as non-responders.

[a] Biochemical response is defined as 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. The ULN for ALP was defined as 116 U/L. The ULN for TB was defined as 1.1 mg/dL.

[b] P-values were obtained using the Cochran–Mantel–Haenszel test stratified by baseline ALP level (< 350 U/L versus ≥ 350 U/L) and baseline pruritus Numerical Rating Scale (NRS) (< 4 versus ≥ 4).

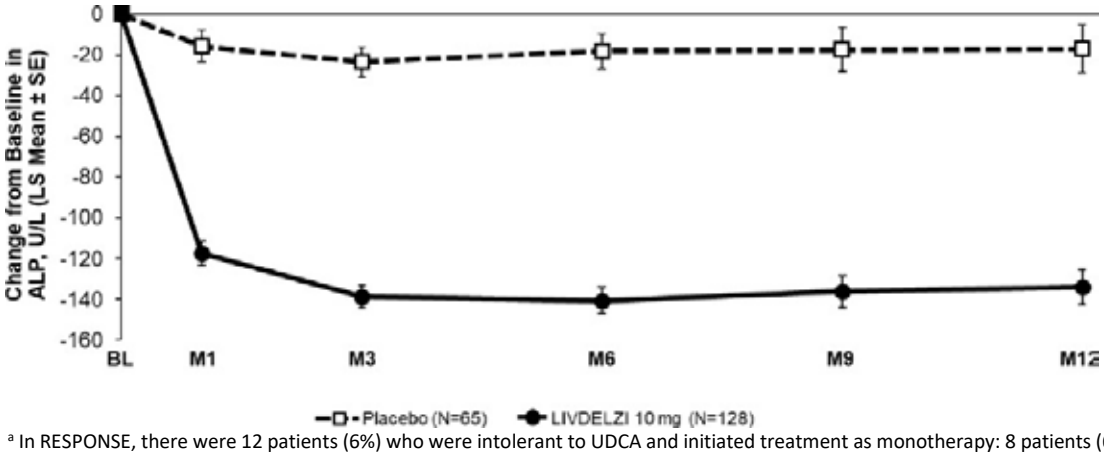
[c] ALP normalization is defined as ALP less than or equal to ULN.

[d] 95% unstratified Miettinen and Nurminen confidence intervals (CIs) are provided.

Mean Reduction in ALP

Figure 1 shows the mean reductions in ALP over 12 months in LIVDELZI-treated patients compared to placebo-treated patients. Reductions were observed at Month 1, continued through Month 6, and were sustained through Month 12. The Least Squares (LS) mean (SE) change from baseline in ALP at Month 12 was -134 (-151, -117) U/L and -17 (-40, 6) U/L in the LIVDELZI 10 mg and placebo arms, respectively. In this trial, rapid and sustained reductions in the alkaline phosphatase level were observed in patients receiving seladelpar.

Figure 1: Change from Baseline in ALP over 12 Months in RESPONSE by Treatment Arm with or without UDCAa



[a] In RESPONSE, there were 12 patients (6%) who were intolerant to UDCA and initiated treatment as monotherapy: 8 patients (6%) in the LIVDELZI 10 mg arm and 4 patients (6%) in the placebo arm.

Among the subset of patients with ALP < 350 U/L at baseline, 76% (71/93) and 23% (11/47) of patients achieved a response at Month 12, in the LIVDELZI 10 mg and placebo arms, respectively. For patients with ALP ≥ 350 U/L at baseline, 23% (8/35) and 11% (2/18) of patients achieved a response at Month 12, in the LIVDELZI 10 mg and placebo arms, respectively.

Mean Reduction in Other Liver Biochemistries: GGT, ALT, and AST

The LS mean (SE) reduction in GGT, ALT, and AST was -108 (8.5), -12 (1.6), and -2.5 (1.3) U/L, respectively, in the LIVDELZI 10 mg arm; and -18 (12), -3.9 (2.2), and -1.5 (1.8) U/L, respectively, in the placebo arm at Month 12. Among the subset of patients with ALT > 1 x ULN at baseline, 56% (40/71) and 25% (9/36) of patients achieved ALT normalization at Month 12, in the LIVDELZI 10 mg and placebo arms, respectively.

In the ASSURE study, the long-term maintenance of biochemical effects was sustained through Month 24 of treatment with LIVDELZI.

Monotherapy

Biochemical response at Month 3 comparing LIVDELZI as a monotherapy to placebo was evaluated in a pooled analysis of a subset of patients from RESPONSE and ENHANCE (a randomized, double-blind, placebo-controlled trial in a similar patient population). Sixty-two percent (62%; 8/13) of LIVDELZI-treated patients achieved a response on the composite endpoint, compared to 17% (1/6) of placebo-treated patients.

Pruritus

LIVDELZI significantly reduced pruritus compared to placebo at Month 6 in patients with baseline average pruritus scores ≥ 4 as assessed by the pruritus Numerical Rating Scale (NRS), a key secondary endpoint in the RESPONSE trial (Table 5). LIVDELZI led to decreased patient-reported pruritus intensity by Month 1, which continued to decrease through Month 6 and was sustained through Month 12 (Figure 2).

Table 5: Change from Baseline in Pruritus NRS over Time in the RESPONSE Trial in PBC Subjects with Moderate to Severe Pruritus at Baselinea

Visit	LIVDELZI 10 mg (N=128)	Placebo (N=65)	LS Mean of Difference (95% CI)
Baseline, n	49	23	
Mean (SD)[b]	6.1 (1.42)	6.6 (1.44)	
Month 1, n	48	22	
LS Mean (SE)	-1.8 (0.23)	-0.8 (0.34)	-1.0 (-1.8, -0.2)
Month 3, n	46	22	
LS Mean (SE)	-2.6 (0.30)	-1.6 (0.43)	-1.0 (-2.1, 0.0)
Month 6[c], n	45	20	
LS Mean (SE)	-3.2 (0.28)	-1.7 (0.41)	-1.5 (-2.5, -0.5)[d]
Month 9, n	36	20	

Visit	LIVDELZI 10 mg (N=128)	Placebo (N=65)	LS Mean of Difference (95% CI)
LS Mean (SE)a	-3.3 (2.35)	-1.9 (1.93)	-1.8 (-2.9, -0.6)
Month 12, n	39	16	
LS Mean (SE)a	-3.4 (2.33)	-1.8 (2.01)	-1.8 (-3.0, -0.6)

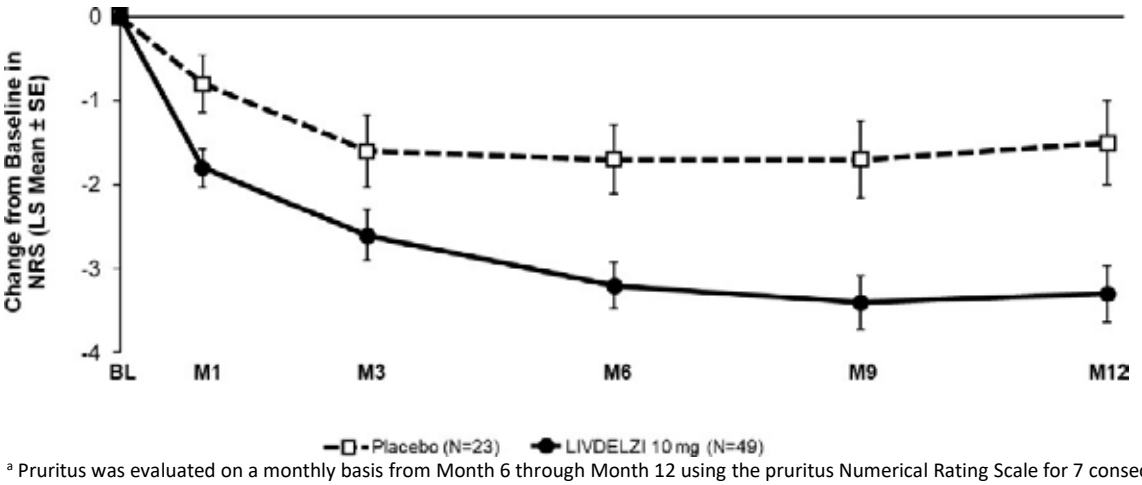
[a.] Assessed using the pruritus NRS, which evaluated patients' daily worst itching intensity on an 11-point rating scale with scores ranging from 0 ("no itching") to 10 ("worst itching imaginable"). The pruritus NRS was administered daily in a ≥ 14-day run-in period prior to randomization through Month 6. Moderate to severe pruritus was defined as a pruritus NRS score ≥ 4.

[b.] Baseline included mean of all daily recorded scores during the run in-period and on Day 1. The pruritus scores for each patient for post-baseline months were calculated by averaging the pruritus NRS scores within the scheduled week each month

[c.] Based on LS means from a mixed-effect model for repeated measures (MMRM) for change from baseline at Months 1 (Week 4), 3 (Week 12), and 6 (Week 26) accounting for baseline average pruritus score, baseline ALP level (< 350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction.

[d] p < 0.05 vs placebo

Figure 2: Change from Baseline in Pruritus NRS over Time in RESPONSE in PBC Patients with Moderate to Severe Pruritus at Baselinea, b



[a] Pruritus was evaluated on a monthly basis from Month 6 through Month 12 using the pruritus Numerical Rating Scale for 7 consecutive days each month.

[b] Based on LS means from a mixed-effect model for repeated measures (MMRM) for change from baseline at Months 1 (Week 4), 3 (Week 12), 6 (Week 26), 9 (Week 39), and 12 (Week 52) accounting for baseline average pruritus score, baseline ALP level (< 350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction. The LS mean (SE) change from baseline in pruritus score at Month 12 was -3.3 (0.33) and -1.5 (0.50) in the LIVDELZI 10 mg and placebo arms, respectively (mean difference [95% CI]: -1.8 [-3.0, -0.6]).

The number (%) of patients who achieved an improvement of 4 points or more on the pruritus NRS scale at Months 6 and 12 were 14 (29%) and 15 (31%) in the LIVDELZI 10 mg arm, respectively, and 4 (17%) and 2 (9%) in the placebo arm, respectively.

The effect of LIVDELZI on pruritus was also demonstrated by additional patient-reported outcome measures in RESPONSE. At Month 6, LIVDELZI-treated patients demonstrated an improvement in pruritus, as observed by reductions in total scores of the PBC-40 Itch Domain and 5-D Itch scale, compared to placebo-treated patients (Table 6). This effect was sustained through Month 12.

Table 6: Change from Baseline in PBC-40 Itch Domain and 5-D Itch Scale Total Scores at Month 6 in RESPONSE in PBC Patients with Moderate to Severe Pruritus at Baseline

	LIVDELZI 10 mg Once Daily (N=49)	Placebo (N=23)	Treatment Difference % (95% CI)
PBC-40 Itch Domain[a]			
Mean (SE)	-2.2 (0.38)	-0.40 (0.60)	-1.8 (-3.2, -0.39)
5-D Itch Scale[b]			
Mean (SE)	-4.7 (0.53)	-1.3 (0.80)	-3.4 (-5.3, -1.5)

[a] LS means were obtained using MMRM for change from baseline at Month 6 accounting for baseline PBC-40 Quality of Life Itch Domain score, baseline ALP level (< 350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction.

[b] LS means were obtained using MMRM for change from baseline at Month 6 accounting for baseline 5-D Itch scale, baseline ALP level (< 350 U/L versus ALP level ≥ 350 U/L), time (in months), treatment arm, and treatment-by-time interaction.

In patients with moderate to severe pruritus at baseline in the RESPONSE trial, LS mean (SE) changes from baseline in the PBC-40 Quality of Life sleep disturbance item (an exploratory endpoint) at Month 6 were -0.53 (0.17) and -0.04 (0.27) in the LIVDELZI 10 mg and placebo arms, respectively (mean difference [95% CI]: -0.48 [-1.12, 0.16]). The LS mean (SE) changes from baseline in the 5-D Itch sleep item score (an exploratory endpoint) at Month 6 were -1.0 (0.16) and -0.3 (0.24) in the LIVDELZI 10 mg and placebo arms, respectively (mean difference [95% CI]: -0.7 [-1.3, -0.2]).

The RESPONSE trial confirms the broad spectrum effect (or profile) LIVDELZI has across the following endpoints: ALP reduction, ALP normalisation, ALT reduction, and improvement in pruritus.

Lipid Parameters

In RESPONSE, decreases from baseline were observed in LIVDELZI-treated patients for the lipid parameters total cholesterol, low density lipoprotein cholesterol (LDL-C), and triglycerides at Month 12. The LS mean difference from placebo in total cholesterol, LDL-C, and triglycerides was -4.4 (95% CI: -8.5, -0.3) mg/dL, -9.0 (95% CI: -15.0, -2.9) mg/dL, and -15.1 (95% CI: -22.1, -8.1), respectively. High density lipoprotein-cholesterol remained stable on treatment with LIVDELZI.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of a single dose of LIVDELZI 10 mg, the median time to peak concentration (T_{max}) was 1.5 hours for seladelpar.

Seladelpar systemic exposure increased dose-proportionally from 2 mg (0.2 times the recommended dosage) to 15 mg (1.5 times the recommended dosage) and greater than dose proportionally at higher doses. For a dose increase from 10 mg to 200 mg (20 times the recommended dosage), mean C_{max} and mean AUC for seladelpar increased 70-fold and 27-fold, respectively.

Following once daily dosing, seladelpar steady-state was achieved by Day 4 and AUC increase was less than 30%. In PBC patients, mean (CV) C_{max} and AUC for seladelpar was 90.5 (42.5%) ng/mL and 817 (44%) ng*h/mL, respectively at steady state following once daily dosing of 10 mg. No clinically significant differences in seladelpar pharmacokinetics were observed following administration of a

high-fat meal in healthy subjects (see Section 4.2 *Dose and method of administration*).

Distribution

In PBC patients, seladelpar steady state apparent volume of distribution was approximately 110.3 L. Seladelpar plasma protein binding is greater than 99%.

Metabolism

Seladelpar is primarily metabolized in vitro by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4, resulting in the three major metabolites: seladelpar sulfoxide (M1), desethyl-seladelpar (M2), and desethyl-seladelpar sulfoxide (M3). The metabolite-to-parent AUC ratios were 0.36, 2.32 and 0.63 for M1, M2 and M3, respectively. Median Tmax for metabolites were 10 hours for M1 and 4 hours for M2 and M3. None of the major metabolites have any clinically relevant pharmacological activity.

Seladelpar plasma exposures (dose-normalized AUC0-inf) were 18% higher in CYP2C9 intermediate metabolizers (*1/*2, *1/*8, *1/*3, *2/*2, N=28) compared to CYP2C9 normal metabolizers (*1/*1, N=84) after a single dose of seladelpar (1 mg to 15 mg). No conclusions could be made for poor metabolizers, as only two subjects with *2/*3 and no subjects with *3/*3 were identified. A 47% increase in dose-normalized $AUC_{0\text{-}inf}$ was seen in individuals who were CYP2C9 poor metabolizers (*2/*3, n=2) compared to CYP2C9 normal metabolizers.

Excretion

In PBC patients, the apparent oral clearance of seladelpar is 12.6 L/h. Following administration of a single dose of 10 mg seladelpar in healthy subjects, mean elimination half-life was 6 hours for seladelpar. In PBC patients, the half-life range was 3.8 to 6.7 hours for seladelpar.

Seladelpar is primarily eliminated in urine as metabolites. Following a single oral dose of 10 mg radiolabeled seladelpar in humans, approximately 73.4% of the dose was recovered in urine (less than 0.01% unchanged) and 19.5% in faeces (2.02% unchanged) within 216 hours.

Pharmacokinetics in special populations

Age, Weight, Gender and Race

No clinically significant differences in the pharmacokinetics of seladelpar were observed based on age (19 to 79 years old), weight (45.8 to 127.5 kg), sex, and race (White, Black, Asian, or other).

Hepatic impairment

Following a single oral dose of 10 mg seladelpar, seladelpar AUC increased 1.1-fold in patients with mild (Child-Pugh A), 2.5-fold in moderate (Child-Pugh B), and 2.1-fold in severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function. Seladelpar C_{max} increased 1.3-fold in patients with mild (Child-Pugh A), 5.2-fold in moderate (Child-Pugh B), and 5-fold in severe (Child-Pugh C) hepatic impairment. Compared to PBC patients with mild hepatic impairment (Child-Pugh A) without portal hypertension, seladelpar exposures (C_{max}, AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment with portal hypertension and 1.6 to 1.9-fold higher in PBC patients with moderate hepatic impairment (Child-Pugh B) after a single oral dose of 10 mg seladelpar.

Accumulation ratios were less than 1.2-fold in PBC patients with mild hepatic impairment with portal hypertension and PBC patients with moderate hepatic impairment following 10 mg seladelpar once daily dosing for 28 days. (see Sections 4.2 *Dose and method of administration* and 4.4 *Special Warnings and Precautions for Use*).

Renal impairment

In a dedicated clinical study of patients with mild (eGFR ≥ 60 to < 90 mL/min), moderate (eGFR ≥ 30 to < 60 mL/min), and severe (< 30 mL/min and not on dialysis) renal impairment, the $AUC_{0\text{-}inf}$ of seladelpar was 48%, 33%, and 3% greater than in patients with normal renal function, respectively, after administration of a single 10 mg dose of seladelpar. The C_{max} of seladelpar was similar in patients with renal impairment, compared to patients with normal renal function. These differences in seladelpar $AUC_{0\text{-}inf}$ are not considered to be clinically meaningful. The pharmacokinetics of seladelpar have not been studied in patients requiring haemodialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Seladelpar was not mutagenic or clastogenic in a bacterial reverse mutation assay (Ames test), an in vitro clastogenicity assay (mouse lymphoma L5178Y thymidine kinase (Tk) gene mutation assay), and a bone marrow micronucleus test in rats.

Seladelpar does not pose a genotoxic risk in humans.

Carcinogenicity

In 2-year carcinogenicity studies in mice and rats (oral doses up to 20 and 30 mg/kg/day, respectively), treatment-related tumours were observed (hepatocellular carcinomas and adenomas and forestomach squamous cell carcinomas in males of both species; pancreatic acinar cell adenoma and benign testicular interstitial cell tumours in male rats). The forestomach tumours are likely of no clinical relevance to humans and occurred at doses that were associated with exposures 87-fold the clinical AUC at the recommended dose of 10 mg seladelpar. The hepatocellular tumours occurred at doses of ≥5 mg/kg/day in mice and 30 mg/kg/day in rats (0.8 and 64-times the clinical AUC at the recommended dose of 10 mg, respectively). Benign pancreatic acinar cell and testis tumours occurred at doses of 30 mg/kg/day in rats (64-times the clinical AUC at the recommended dose of 10 mg). These tumours are typical of tumours related to rodent-specific PPARα agonism and therefore are unlikely to be clinically relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents:

microcrystalline cellulose
mannitol

croscarmellose sodium
butylated hydroxytoluene
magnesium stearate
silicon dioxide

Capsule shell:

gelatin
titanium dioxide
iron oxide black
iron oxide yellow
iron oxide red
indigo carmine
TekPrint SW-9008 Black ink/TekPrint SW-9009 Black ink (ARTG PI 2328/2343)
TekPrint White SB-0007P White ink (ARTG PI 2216)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Capsules should be used within 30 days after first opening the container.

6.5 NATURE AND CONTENTS OF CONTAINER

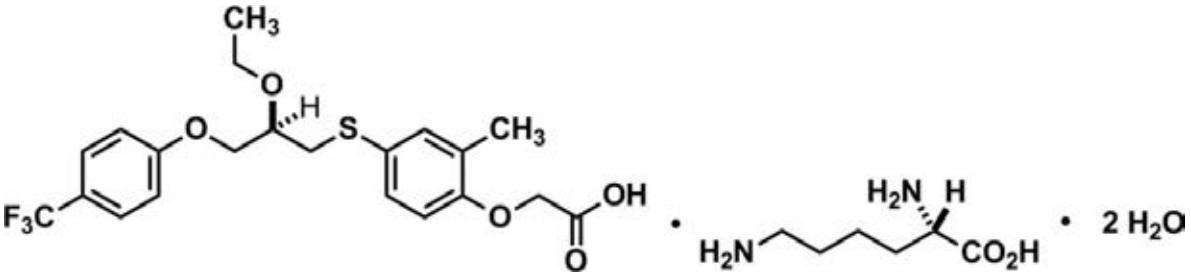
LIVDELZI capsules are packaged in a high-density polyethylene bottle closed with a polypropylene child resistant cap containing an induction seal. Each bottle contains 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



LIVDELZI capsules contain seladelpar a potent and selective PPARδ agonist. Seladelpar is a single enantiomer of the R-configuration and is present as a lysine dihydrate salt. Seladelpar lysine dihydrate is a white to off-white powder with a molecular formula of $C_{21}H_{23}F_3O_5S \bullet C_6H_{14}N_2O_2 \bullet 2H_2O$ and a molecular weight of 626.7 g/mol. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH. The chemical name for seladelpar is 2-[4-[(2R)-2- ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl]sulfanyl-2-methylphenoxy]acetic acid, lysine dihydrate.

CAS number

928821-40-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

TBA

10 DATE OF REVISION

TBA

Summary table of changes

Section Changed	Summary of new information
	New