Livdelzi®
(seladelpar lysine dihydrate) 10 mg)
Per os

1. NAME OF THE MEDICINAL PRODUCT

Livdelzi®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Size 1 (26.1 mm x 9.4 mm) hard capsules with dark blue opaque cap and light grey opaque body imprinted with “CBAY” in white ink on the cap and “10” in black ink 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 Posology and method of administration

Posology

The recommended dose of seladelpar is 10 mg once daily.

Missed dose

If a dose of seladelpar 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

Elderly
Limited data exists in elderly patients. No dose adjustment is required for elderly patients (see section 5.2).

Renal impairment
No dose adjustment of seladelpar is required for patients with mild, moderate and severe renal impairment (see section 5.2).

Patients with end-stage renal disease on dialysis have not been studied. No dose recommendation can be provided for this group.

Hepatic impairment
No dose adjustment is required in PBC patients with mild hepatic impairment (Child-Pugh A).

Safety and efficacy of seladelpar have not been established in PBC patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.
Use of seladelpar is not recommended in patients with severe hepatic impairment and 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 seladelpar if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C)(see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of seladelpar in the paediatric population in the treatment of PBC.

Method of administration

Oral use. The capsules can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Liver test abnormalities

Dose dependent increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) have been observed in patients receiving higher doses of seladelpar (see section 4.9). Obtain baseline clinical and laboratory assessments at initiation of treatment with seladelpar and monitor thereafter according to routine clinical practice. Consider temporary interruption of seladelpar treatment if liver tests worsen, or the patient develops signs and symptoms consistent with liver dysfunction. Consider permanent discontinuation if liver tests worsen again after restarting seladelpar.

Biliary Obstruction

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

Co-administration of other medicinal products

Co-administration of probenecid with seladelpar is not recommended (see section 4.5).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on seladelpar

Probenecid

Concomitant administration of seladelpar with probenecid (an OAT1, OAT3 and OATP1B1-inhibitor) is not recommended (see section 4.4).

In a dedicated clinical drug interaction study, seladelpar area under the curve from zero to time infinity ($AUC_{0\text{-}inf}$) increased by 2-fold and maximum serum concentration (C_{max}) by 4.69-fold following concomitant use of a single 10 mg seladelpar dose with 500 mg probenecid in healthy subjects.

Inhibitors of drug transporters

Concomitant administration of seladelpar with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3 and OAT3 (e.g cyclosporine) may result in an increase of seladelpar exposure. When seladelpar is concomitantly administered with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3, and OAT3, patients should be closely monitored for adverse effects.

In a dedicated clinical drug interaction study, 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 (a BCRP, OATP1B1, OATP1B3 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 and CYP3A4 inhibitors

Seladelpar is primarily metabolized *in vitro* by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. Concomitant administration of seladelpar with medicines that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate-to-strong CYP3A4 inhibitors may result in an increase in seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors (e.g. fluconazole, mifepristone), patients should be closely monitored for adverse effects.

In a dedicated clinical drug interaction study, 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 (moderate CYP2C9 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 inducers and strong CYP3A4 inducers

Concomitant administration of seladelpar with medicines that are CYP2C9 inducers and strong CYP3A4 inducers (e.g. rifampicin, a strong CYP3A4 and moderate CYP2C9 inducer) can decrease seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are CYP2C9 inducers and strong CYP3A4 inducers, patients should be monitored for a potential reduction in efficacy.

Seladelpar $AUC_{0\text{-}inf}$ decreased by approximately 44% and C_{max} by 24% following administration of a single 10 mg seladelpar dose after carbamazepine 300 mg twice daily in healthy subjects. The carbamazepine (a strong CYP3A and weak CYP2C9 inducer) dose was escalated from 100 mg to 300 mg over 7 days.

Bile acid binding resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam, 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

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of seladelpar in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposure levels (see section 5.3).

As a precautionary measure**,** it is preferable to avoid the use of seladelpar during pregnancy.

Breast-feeding

It is unknown whether seladelpar or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from seladelpar therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of seladelpar on fertility are available.

Animal studies do not indicate any direct or indirect effects on fertility or the ability to reproduce.

4.7 Effects on ability to drive and use machines

Seladelpar has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

Based on clinical trial experience, the most frequently reported adverse reactions were abdominal pain (11.1%), headache (7.2%), nausea (6.5%) and abdominal distension (3.9%). These adverse reactions were non-serious and did not lead to discontinuation of seladelpar.

Tabulated list of adverse reactions

The frequencies of the adverse drug reactions provided in the table below are based on pooled data from the RESPONSE and ENHANCE trials unless otherwise stated.

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 1: Adverse drug reactions reported in clinical trials in patients treated with seladelpar

System Organ Class	Very Common	Common
Nervous System Disorders		Headache
Gastrointestinal Disorders	Abdominal pain[a]	Nausea Abdominal distension

a Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects, or by clicking on the link: https://sideeffects.health.gov.il/

4.9 Overdose

PBC patients who received 5 times the recommended dose or 20 times the recommended dose of seladelpar experienced an increase in liver transaminases, muscle pain, and/or elevations in creatine phosphokinase, which resolved upon seladelpar discontinuation. Dose dependent increases in serum creatinine were also observed.

There is no specific treatment for overdose with seladelpar. General supportive care of the patient is indicated, as appropriate. If indicated, elimination of unabsorbed medicinal product 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, other drugs for bile therapy. ATC code: A05AX07

Mechanism of action

Seladelpar is a peroxisome proliferator-activated receptor delta (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.

Pharmacodynamic effects

In clinical studies, reduction in ALP was observed within 1 week, continued to decrease through Month 3, and was sustained through Month 24.

In RESPONSE, treatment with seladelpar led to a decrease in Interleukin-31 (IL-31) after 6 and 12 months of treatment in patients with moderate to severe pruritus.

Clinical efficacy and safety

The efficacy of seladelpar was evaluated in patients with PBC in a randomised, double-blind, placebo-controlled, 12-month trial (RESPONSE). Patients were included in the trial if their ALP was 1.67-times upper limit of normal (ULN) or greater and total bilirubin was less than or equal to 2-times 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 oesophageal varices or history of variceal bleeds, history of hepatorenal syndrome). A 14-day run-in period prior to randomisation was used to establish a baseline itch intensity, as measured by the

patient-reported daily 24-hour Numerical Rating Scale (Pruritus-NRS) scores (0 “no itch” to 10 “worst itch imaginable”).

Patients were randomised (2:1) to receive either seladelpar (n = 128) 10 mg once daily; or placebo (n = 65) for 12 months. Seladelpar 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 two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Of the 193 randomised patients, the mean age was 56.7 years (range 28-75 years); 41 (21%) were aged 65 years or older; 183 (95%) were female; 170 (88%) were White, 11 (6%) were Asian, 4 (2%) were Black or African American, 6 (3%) were American Indian or Alaska Native. A total of 56 (29%) patients identified as Hispanic/Latino.

The mean baseline ALP concentration was 314.3 U/L, corresponding to 2.7-times ULN. The mean baseline total bilirubin concentration was 0.758 mg/dL and was less than or equal to the ULN in 87% of the enrolled patients. At baseline patients in the study population had the following elevations in other liver biochemistries: alanine aminotransferase (ALT) 1.2-times the ULN, aspartate aminotransferase (AST) 1.2-times the ULN, and gamma-glutamyl transferase (GGT) 1.7-times the ULN. The baseline mean (SD) pruritus NRS score was 3.0 (2.85). Among enrolled patients, 49 (38%, mean NRS score 6.1) in the seladelpar 10 mg arm and 23 (35%, mean NRS score 6.6) in the placebo arm had moderate to severe pruritus (NRS score ≥ 4) at baseline (mean baseline NRS score 6.3).

Cirrhosis (Child-Pugh A) was present at baseline in 18 patients (14%) in the seladelpar 10 mg arm, and 9 patients (14%) in the placebo arm.

In RESPONSE, the primary endpoint was a responder analysis at Month 12, where response was defined as a composite of three criteria: ALP less than 1.67-times the ULN, total bilirubin ≤ ULN, and an ALP decrease of at least 15%. The ULN for ALP was defined as 116 U/L for females and males. The ULN for total bilirubin was defined as 1.1 mg/dL for females and males. ALP normalisation was defined as achieving ALP less than ≤ 1.0-times the ULN. The pruritus improvement was assessed by change from baseline in weekly averaged pruritus NRS score at Month 6 in patients with NRS score ≥ 4 at baseline.

The results for the primary composite endpoint and ALP normalisation are presented in Table 2.

Table 2: RESPONSE trial: Composite biochemical endpoint and ALP normalisation with seladelpar with or without UDCA[a]

	Seladelpar 10 mg (N = 128)	**Placebo (N = 65)**	**Treatment difference % (95% CI)[e]**
Primary composite endpoint at Month 12[b]			
Responder rate, (%)[c] [95 % CI]	62 [53, 70]	20 [10, 30]	42 (28, 53)
Components of primary endpoint			
ALP less than 1.67-times ULN, (%)	66	26	39 (25, 52)
Decrease in ALP of at least 15%, (%)	84	32	51 (37, 63)
Total bilirubin less than or equal to ULN[d], (%)	81	77	4 (-7, 17)
ALP normalisation			
ALP normalisation at Month 12, ≤ 1.0×ULN (%)[c] [95% CI]	25 [18, 33]	0 [0, 0]	25 (18, 33)

N = Number

CI = Confidence Interval

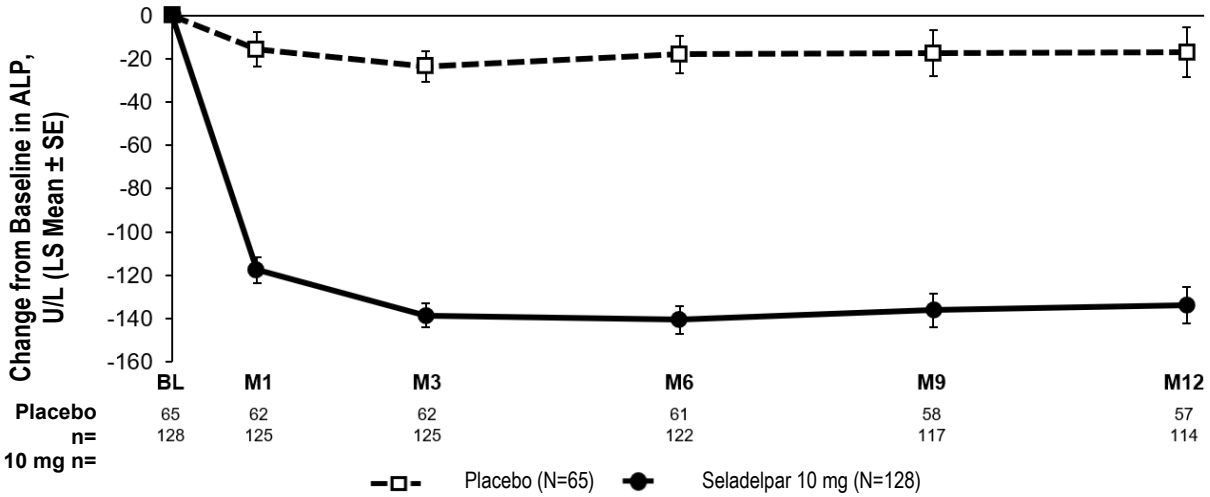
a In the trial there were 12 patients (6%) who were intolerant to UDCA and initiated treatment as monotherapy: 8 subjects (6%) in the seladelpar 10 mg arm, and 4 patients (6 %) in the placebo arm.

b Percentage of patients achieving a response, defined as an ALP value less than 1.67-times the ULN, an ALP decrease of at least 15%, and total bilirubin less than or equal to the ULN. Patients with missing values were considered as not achieving response.
c $p < 0.0001$ for seladelpar 10 mg versus placebo. P-value was obtained using the Cochran–Mantel–Haenszel Test stratified by baseline ALP level < 350 U/L versus ALP level ≥ 350 U/L, and baseline pruritus NRS < 4 versus ≥ 4.
d The mean baseline total bilirubin value was 0.758 mg/dL and was less than or equal to the ULN in 87% of the enrolled patients.
e 95% unstratified Miettinen and Nurminen confidence intervals (CIs) are provided.

Alkaline phosphatase (ALP)

Figure 1 shows the mean reductions in ALP in seladelpar-treated patients compared to placebo. Reductions were observed at Month 1, continued through Month 6, and were sustained through Month 12.

Figure 1: Change from baseline in ALP over 12 months in RESPONSE by treatment arm with or without UDCA[a]



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

Among the subset of patients with ALP < 350 U/L (< approximately 3-times ULN) at baseline, 76% (71/93) and 23% (11/47) of patients achieved a response at Month 12, in the seladelpar 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 seladelpar 10 mg and placebo arms, respectively.

Lipid Parameters

The LS means difference from placebo in percentage change from baseline 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 at month 12. High density lipoprotein-cholesterol remained stable on treatment with seladelpar.

Pruritus

Seladelpar significantly reduced pruritus compared to placebo at Month 6 in patients with baseline average pruritus scores ≥ 4 as assessed by pruritus NRS score, a key secondary endpoint in the RESPONSE trial (Table 3). Seladelpar led to decreased patient-reported pruritus intensity by Month 1 which continued to decrease to Month 6.

Table 3. Change from Baseline in Pruritus Score at Month 6 in RESPONSE in PBC Patients with Moderate to Severe Pruritus at Baseline[a]

	Seladelpar 10 mg (N=49)	Placebo (N=23)	Treatment difference % (95% CI)
Baseline average pruritus score, Mean (SD)[b]	6.1 (1.4)	6.6 (1.4)	-
Change from baseline in pruritus score at Month 6[c]			
Mean (SE)	-3.2 (0.28)	-1.7 (0.41)	-1.5 (-2.5, -0.5)[d]

[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] $p < 0.005$ for seladelpar 10 mg versus placebo.

The effect of seladelpar on pruritus was also assessed by additional patient-reported outcome measures in RESPONSE. At Month 6, an improvement in pruritus, as observed by reductions in total scores of the PBC-40 Itch Domain and 5-D Itch scale, was seen with seladelpar. (Table 4).

Table 4. 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

	Seladelpar 10 mg (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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single dose of seladelpar 10 mg, seladelpar was readily absorbed with median time to peak concentration (t_{max}) of approximately 1.5 hours.

Seladelpar exposure increased approximately dose-proportionally with single doses from 2 mg to 15 mg, after which the increase in C_{max} was larger than dose-proportional.

Seladelpar showed no evidence of meaningful drug accumulation after multiple daily dosing, and steady-state was achieved from day 4 onwards after daily dosing.

Co-administration of seladelpar with food delayed the t_{max} by 2.5 hours relative to fasted conditions and resulted in an approximately 32% reduction in the C_{max} of seladelpar. As the overall exposure (AUC) is similar, the effects of food on seladelpar pharmacokinetics are not considered clinically relevant.

Distribution

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

Biotransformation

Seladelpar is primarily metabolized by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. M2 is a major metabolite observed in human plasma, accounting for 17.6% of the total plasma radioactivity in the mass balance study and approximately doubling the plasma exposure compared to seladelpar. M2 is not expected to have clinically relevant pharmacological effects.

Elimination

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.

Following administration of an oral dose of radiolabelled seladelpar, 92.9% of radioactivity was recovered: 73.4% in urine and 19.5% in faeces. Urinary excretion of the dose as unchanged seladelpar was negligible (less than 0.01%).

Characteristics in specific groups or special populations

CYP2C9 genotype
Seladelpar is primarily metabolised *in vitro* by CYP2C9 which is a polymorphic enzyme. Seladelpar plasma exposure (dose-normalised $AUC_{0\text{-}inf}$) was 18% higher in CYP2C9 intermediate metabolisers (*1/*2, *1/*8, *1/*3, *2/*2, n=28) compared to CYP2C9 normal metabolisers (*1/*1, n=84) after a single dose of seladelpar 1 mg to 15 mg. No conclusion could be made for poor metabolisers due to only one identified subject with *2/*3 and no subjects with *3/*3 were identified.

Age, weight, gender and race
Based on population pharmacokinetic analysis, age (19 to 79 years old), weight (45.8 to 127.5 kg), gender, and race (White, Black, Asian, other) do not have a clinically meaningful effect on the pharmacokinetics of seladelpar. No dose adjustments are warranted based on these factors.

Renal impairment
In a dedicated clinical study of patients with mild (eGFR $\geq$ 60 to < 90 mL/min), moderate (eGFR $\geq$ 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. No dose adjustment of seladelpar is required for patients with mild, moderate, or severe renal impairment.

The pharmacokinetics of seladelpar have not been studied in patients requiring haemodialysis.

Hepatic impairment
Based on a clinical pharmacology study in subjects with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, and C, respectively), seladelpar AUC was increased 1.10, 2.52, and 2.12-fold, and C_{max} was increased 1.33, 5.19, and 5.03-fold, respectively, compared to subjects with normal hepatic function.

In an additional study, seladelpar exposures (C_{max}, AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment (Child-Pugh A) with portal hypertension, 1.6 to 1.9-fold higher in PBC patients with moderate hepatic impairment (Child-Pugh B), and 2.1 to 2.5-fold higher in PBC patients with severe hepatic impairment (Child-Pugh C), compared to PBC patients with mild hepatic impairment without portal hypertension, after a single oral dose of 10 mg seladelpar.

Following administration of 10 mg seladelpar once daily for 28 days in PBC patients with mild hepatic impairment (Child-Pugh A) with portal hypertension and PBC patients with moderate hepatic impairment (Child-Pugh B), there was no clinically meaningful accumulation of seladelpar (accumulation ratios were less than 1.2-fold).

Drug interaction studies

Effect of seladelpar on other medicinal products
Seladelpar has no clinically relevant effect on the pharmacokinetics of tolbutamide (CYP2C9 substrate), midazolam (CYP3A4 substrate), simvastatin (CYP3A4 and OATP substrate), atorvastatin (CYP3A4 and OATP substrate), and rosuvastatin (BCRP and OATP substrate).

Effect of other medicinal products on seladelpar
P-gp inhibitor
In a dedicated clinical drug interaction study, seladelpar exposures were not significantly altered when a single dose of 600 mg quinidine (a P-gp inhibitor) was co-administered in healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development.

Reproductive and developmental toxicity

Seladelpar did not cause any foetal malformations or effects on embryo-foetal survival or growth in rats or rabbits. In rats, the exposure at NOAEL was 145-fold higher than the clinical AUC at the recommended dose of 10 mg, and 2-fold the clinical AUC in rabbits.

Oral administration of seladelpar at doses of 0, 5, 20 or 100 mg/kg/day in rats 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 at the NOAEL of 20 mg/kg/day was 15-fold the clinical AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Mannitol (Pearlitol 200 SD)
Microcrystalline cellulose (Avicel PH 302, Avicel PH 101)
Croscarmellose sodium (Ac-di-sol)
Magnesium stearate (Hyqual, vegetable source)
Colloidal silicon dioxide (Cab-O-Sil M5P)
Butylated hydroxytoluene

Capsule shell

Gelatin
Titanium dioxide
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
FD&C Blue #2

Black ink used to imprint “10” (on the body of the capsule shell contains)

Shellac (E904)
Propylene glycol (E1520)
Purified water
Potassium hydroxide (E525)
Black iron oxide irradiated (E172)

White ink used to imprint “CBAY” (on the cap of the capsule contains)

Shellac (E904)
Propylene glycol (E1520)
Sodium hydroxide (E524)
Povidone (E1201)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C until end of shelf life.

6.5 Nature and contents of container

Livdelzi hard 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 and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

8. REGISTRATION HOLDER

Gilead Sciences Israel Ltd.
4 HaHarash Street
Hod Hasharon Business Park
4524075
Israel

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in December 2025.

IL-DEC25-EU-OCT25