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Livdelzi® (seladelpar) Use in Renal Impairment

This document is in response to your request for information regarding Livdelzi® (seladelpar [SEL]) and its use in patients with renal impairment (RI).

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Product Labeling[1]

The recommended dosage in patients with mild, moderate, or severe RI is the same as in patients with normal renal function. Patients with end-stage renal disease on dialysis have not been studied.

In subjects with mild (eGFR ≥60 to <90 mL/min/1.73 m^2, MDRD), moderate (eGFR ≥30 to <60 mL/min/1.73 m^2), and severe (<30 mL/min/1.73 m^2 and not on dialysis) RI, the AUC_{inf} of SEL was 10% higher, 54% higher, and similar to that in subjects with normal renal function, respectively, after administration of a single 10 mg dose of SEL. The difference in C_{max} of SEL was less than 18% in subjects with renal impairment compared to subjects with normal renal function. The PKs of SEL have not been studied in patients requiring hemodialysis.

Clinical Data on the Use of SEL in RI

Phase 1 PK Study

Study design and demographics[2]

CB8025-11942, a phase 1 study, was conducted to compare the PK parameters, safety, and tolerability of a single dose of SEL 10 mg in participants with mild ($eGFR_{MDRD}$ ≥60 to <90 mL/min/1.73 m^2), moderate ($eGFR_{MDRD}$ ≥30 to <60 mL/min/1.73 m^2), or severe ($eGFR_{MDRD}$ <30 mL/min/1.73 m^2) RI with those of matched healthy volunteers ($eGFR_{MDRD}$ ≥90 mL/min/1.73 m^2). Participants who required hemodialysis were excluded. Samples from blood and urine were collected pre- and postdose (for 3 and 2 days after the single dose, respectively).

Table 1. Baseline Demographics and Disease Characteristics (Zhou et al)[2]

Key Demographics and Characteristics	Normal Renal Function (n=12)	Mild RI (n=8)	Moderate RI (n=8)	Severe RI (n=8)
Age, mean (SD), years	58.9 (7.3)	65.4 (5)	63.8 (8.6)	65.6 (9.5)
Female, n (%)	4 (33)	2 (25)	3 (38)	2 (25)

Key Demographics and Characteristics	Normal Renal Function (n=12)	Mild RI (n=8)	Moderate RI (n=8)	Severe RI (n=8)
Race, White/Black or African American, n (%)	10 (83)/2 (17)	8 (100)/0	7 (88)/1 (13)	8 (100)/0
Weight, mean (SD), kg	82.4 (11.4)	85.2 (16.1)	84.6 (9.3)	93.7 (10.7)
BMI, mean (SD), kg/m^2	30.3 (2.7)	28.9 (3.2)	31.1 (2.6)	32.5 (2)
eGFR, mean (SD), mL/min/1.73 m^2	90.7 (13.9)	73 (5.6)	49.6 (9.2)	23.7 (8.5)

PK results

SEL-treated participants with mild RI had increases of total SEL AUC_{0-t} and C_{max} by up to 13% and 17%, respectively, compared with those observed for healthy volunteers (Table 2). SEL-treated participants with moderate RI had an increase of 59% in total SEL AUC_{0-t} and no increases in total SEL C_{max} compared with healthy volunteers (Table 2). SEL-treated participants with severe RI had AUC_{0-t} and C_{max} values comparable to those of healthy volunteers (Table 2). Changes were not considered clinically meaningful; thus, dose adjustment for RI is not needed.[2]

Table 2. PK Parameters by Severity of RI for Participants Matched With Healthy Volunteers (Zhou et al)[2]

Parameters, Mean (SD)	Mild RI vs Matched Normal (Each, n=8)			Moderate RI vs Matched Normal (Each, n=8)			Severe RI vs Matched Normal (Each, n=8)		
	Normal Renal Function	Mild RI	GLSMR (90% CI)	Normal Renal Function	Moderate RI	GLSMR (90% CI)	Normal Renal Function	Severe RI	GLSMR (90% CI)
AUC_{0-t}, h·ng/mL	628 (277.87)	689.5 (203.8)	1.13 (0.82–1.57)	567.8 (151.3)	961.4 (511.29)	1.59 (1.15–2.2)	605.2 (126.74)	645.5 (422.05)	0.95 (0.69–1.31)
AUC_{0-inf}, h·ng/mL	670 (267.36)	725.6 (219.95)	1.1 (0.81–1.49)	606.3 (132.48)	1005.8 (556.88)[a]	1.52 (1.08–2.14)	637.1 (120.44)[a]	693.8 (427.38)	1.01 (0.71–1.44)
C_{max}, ng/mL	69.3 (14.65)	85.6 (33.37)	1.17 (0.85–1.63)	83.8 (36.1)	85.8 (40.74)	0.99 (0.69–1.44)	82 (37.64)	86.8 (45.07)	1.01 (0.66–1.55)
T_{max},[b] h	2.8 (1–4)	2 (0.5–6)	–	2.6 (1–4)	2.8 (1–10)	–	2.8 (1–10)	3.3 (1–6)	–
$T_{1/2}$, h	5.1 (1.47)	4.8 (1.18)	–	4.7 (0.6)	7.9 (3.04)	–	4.8 (0.6)[a]	5.8 (3.52)	–
Ae_{0-t}, ng	3068.3 (2340.39)[c]	2113.6 (774.17)	–	3068.3 (2340.39)[c]	2583.7 (2701.77)[a]	–	2052.5 (863.86)[c]	1409.1 (1154.96)[c]	–
Cl_R, L/h	0.006 (0.0056)[c]	0.003 (0.0016)	–	0.006 (0.0056)[c]	0.004 (0.005)[a]	–	0.003 (0.0014)[c]	0.002 (0.0016)[c]	–

Abbreviations: $T_{1/2}$=terminal half-life; T_{max}=time to maximum concentration.
[a]n=7. [b]Median (range) is presented. [c]n=4.
Note: Matching by age, sex, and BMI was performed. The same 12 healthy volunteers were used for matching, so they may have been included in >1 group. eGFR was indexed via body surface area.

A post hoc analysis regrouped participants based on absolute eGFR (calculated as eGFR [mL/min/1.73 m^2] × body surface area/1.73 m^2), and PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) were consistent with those obtained using indexed eGFR.[2]

In a regression analysis that evaluated the relationship between eGFR and PK parameters, no correlation was observed for renal function and AUC_{0-inf} (R^2=0.014), C_{max} (R^2=0.002), A_{e0-t} (R^2=0.023), or Cl_R (R^2=0.025). Worsened renal function did not have a clinically meaningful impact on the protein binding of SEL, as the mean percentage fraction of unbound SEL across RI groups was numerically similar to that in participants with normal renal function.[2]

For SEL metabolites, the AUC and C_{max} increased minimally in participants with mild RI and by varying amounts in participants with moderate or severe RI. A regression analysis of SEL

metabolite plasma PK parameters and eGFR determined that there was a trend toward increasing metabolite exposure with decreasing eGFR. There was also trend toward decreasing Cl_R and amounts of excreted SEL metabolites in the urine as renal function worsened.[3]

Additionally, no clear correlation was shown between urine PK parameters and the relationship between SEL plasma exposure and eGFR measurements.[3]

Safety results

Across all treatment groups, 6 participants reported TEAEs: normal renal function, 2 participants (16.7%) reported 2 TEAEs; mild RI, 1 participant (12.5%) reported 1 TEAE; moderate RI, 3 participants (37.5%) reported 5 TEAEs; and severe RI, none were reported.[3] All AEs were classified as mild and were considered unrelated to SEL by the investigator.[2] The most common TEAEs were gastrointestinal disorders (2 participants reported 3 TEAEs: nausea, diarrhea, and toothache) and abnormal laboratory results (2 participants reported 2 TEAEs: abnormal cystatin C and protein in urine). The majority of the TEAEs recovered or were resolved by the end of the study.[3]

There were no deaths, Grade ≥3 AEs, serious AEs, or discontinuations due to an AE; no clinically relevant differences among renal function groups were noted related to laboratory values, vital signs, or ECGs.[2]

Abbreviations

AE=adverse event
Ae_{0-t}=cumulative urinary excretion from time 0 to end of dosing interval
AUC_{0-inf}/AUC_{inf}=area under the concentration-time curve from time 0 to infinity
AUC_{0-t}=area under the concentration-time curve from time 0 to end of dosing interval
Cl_R=renal clearance
C_{max}=maximum concentration
GLSMR=geometric least squares mean ratio
MDRD=Modification of Diet in Renal Disease equation
PK=pharmacokinetic
RI=renal impairment
SEL=seladelpar
TEAE=treatment-emergent adverse event

References

1. Enclosed. LIVDELZI® (seladelpar) capsules, for oral use. US Prescribing Information. Foster City, CA
2. Zhou J, Qi X, McFarlane J, Bhardwaj R, Crittenden DB. Pharmacokinetics, Safety, and Tolerability of Seladelpar in People With Renal Impairment [Poster FRI-317]. Paper presented at: European Association for the Study of the Liver Congress; 7-10 May, 2025; Amsterdam, the Netherlands.
3. Gilead Sciences Inc. Data on File.

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Livdelzi US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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