FILSPARI® (sparsentan)
Drug-Drug Interactions

Summary

Prescribing Information

- FILSPARI is an endothelin and angiotensin II receptor antagonist indicated to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression[1]
- Prior to initiating treatment with FILSPARI, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors and endothelin receptor antagonists (ERAs)[1]
- Some medications should not be used concomitantly with FILSPARI, including ARBs, ERAs, aliskiren, strong CYP3A inhibitors or inducers, acid-reducing agents, and sensitive substrates of P-gp and BCRP[1]
- Use of other medications in conjunction with FILSPARI may require monitoring of blood pressure, serum potassium, edema, and kidney function, including moderate CYP3A inhibitors, NSAIDs, and COX-2 inhibitors[1]

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[2-4]

Study Data

Preclinical Studies

- A study of human hepatocytes demonstrated that sparsentan is not a CYP1A2 inducer but may induce CYP2B6 and CYP3A4[5]
- A study of pooled HLMs suggested that sparsentan has a low probability of causing a DDI by inhibiting the metabolism of a coadministered drug, and sparsentan metabolism was found to be primarily mediated by CYP3A4[6]

Clinical Studies

- A study examining the impact of steady-state sparsentan on the PK of MDZ and BUP found that sparsentan had no impact on MDZ or MDZ-OH PK, indicating no inhibition or induction of CYP3A4[7]
- BUP exposure was reduced with sparsentan, suggesting sparsentan induces CYP2B6[7]
- Population PK analysis found sparsentan $t_{1/2}$ to be 9.6 hours at steady state, apparent Vc/F of 69.5 L, and apparent CL/F of 5.27 L/h after a single 800 mg dose, with relative bioavailability of sparsentan decreasing with increasing dose[8]

- Additional analyses determined that coadministration of CYP3A4 inhibitors increased steady-state AUC, with the effect of strong CYP3A4 inhibitors considered to be clinically meaningful[8]
- A study of multiple sparsentan doses on single-dose PK of the SGLT2 inhibitor dapagliflozin in healthy adults found that sparsentan did not affect dapagliflozin PK[9]

Prescribing Information

Drug Interactions[1]

- Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure)
- Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration. Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. No FILSPARI dose adjustment is needed. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC, which may increase the risk of FILSPARI adverse reactions.
- Avoid concomitant use with strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC, which may reduce FILSPARI efficacy.
- Administer FILSPARI 2 hours before or after administration of antacids
- Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy
- Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure. These effects are usually reversible
- Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates
- Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates
- Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing

diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[2-4] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[10-12]

Preclinical Studies

In studies utilizing human liver microsomes and human hepatocytes, potential DDIs were assessed between sparsentan and other drugs used to treat FSGS. Possible interactions were examined for cyclosporine A, fluvastatin, fenofibrate, voriconazole (as the control CYP3A inhibitor), prednisone, torsemide, atorvastatin, cerivastatin, pravastatin, and simvastatin.[5]

CYP induction potential was examined with human hepatocytes incubated with multiple doses of sparsentan, followed by measurement of mRNA for levels of CYP gene expression, or by measurement of CYP activities using marker substrates phenacetin, bupropion, or testosterone.[5]

Clinical Studies

Clinical studies further evaluated the potential for DDIs with sparsentan use. The effect of steady-state sparsentan on the PK of midazolam and buproprion was conducted in an open-label, single-sequence study of healthy males. Single doses of midazolam and bupropion were given alone and subsequently and concurrently with sparsentan, as indicator probe drugs for CYP450 3A4 and 2B6, respectively.[7] Additionally, population PK data from 9 clinical studies were evaluated to determine the impact of disease characteristics and concomitant medications on the PK of sparsentan in healthy volunteers, volunteers with hepatic impairment, and FSGS patients.[8]

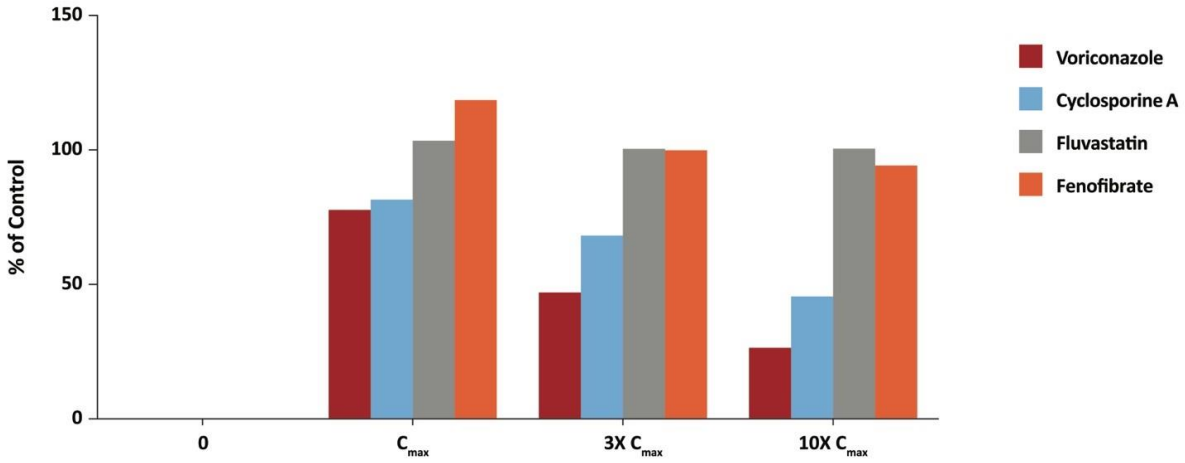
Interactions between multiple doses of sparsentan and single doses of the SGLT2 inhibitor dapagliflozin were assessed in an open-label, 1-sequence crossover study in 22 healthy adults. Subjects were given 10 mg dapagliflozin on study day 1 and subsequently dosed with 800 mg/day sparsentan on days 5-14. A single 10 mg dapagliflozin dose was coadministered on day 11. Dapagliflozin-3-O-glucuronide, an inactive metabolite, was measured as an indicator of uridine 5'-diphosphoglucuronosyltransferase 1A9, the primary metabolizing enzyme of dapagliflozin.[9]

Study Data

Preclinical Studies

In human hepatocyte studies, among 1 out of 3 donors, sparsentan metabolism was enhanced in hepatocytes treated with rifampicin at 20 µM and torsemide at 42 µM (10x C_{max}). Cyclosporine A and voriconazole, but not fluvastatin and fenofibrate, showed concentration-dependent inhibition of sparsentan metabolism (**Figure 1**).[5]

Figure 1. Evaluation of Potential Coadministered Drugs on Sparsentan Metabolism



No effects were observed on sparsentan metabolism in hepatocytes treated by cyclosporine A, prednisone, simvastatin, atorvastatin, cerivastatin, fluvastatin, pravastatin, and flumazenil in all 3 donors. Results of this study suggest that sparsentan is not a CYP1A2 inducer but may induce CYP2B6 and CYP3A4.[5]

The potential of sparsentan to inhibit activities of multiple CYP enzymes was also assessed in pooled HLMs. Based on this assay, the calculated Ki for CYP3A4 equaled 26.9 µM. The IC_{50} of CYP2C8 was 99.2 µM. Across additional tested CYP enzymes, no inhibition was observed. These findings suggest that sparsentan has low probability of causing a DDI by inhibiting the metabolism of a coadministered drug. The metabolism of sparsentan was found to be primarily mediated by CYP3A4.[6]

Clinical Studies

Impact of Sparsentan on Midazolam and Buproprion

In an open-label, single-sequence study, the impact of steady-state sparsentan on the PK of midazolam and bupropion was evaluated. Single doses of 2 mg midazolam and 150 mg bupropion were given alone and subsequently and concurrently with sparsentan in a sample of healthy male volunteers between ages 18-50 years. PK samples were collected and analyzed for midazolam (MDZ), 1-hydroxymidazolam (MDZ-OH), bupropion (BUP), R-bupropion (R-BUP), S-bupropion (S-BUP), (2R,3R)-hydroxybupropion [(2R,3R)-BUP-OH], and (2S,3S)-hydroxybupropion [(2S,3S)-BUP-OH] plasma concentrations.[7]

Sparsentan achieved steady state prior to coadministration with midazolam and bupropion. Sparsentan had no impact on MDZ or MDZ-OH PK, indicating no inhibition or induction of CYP3A4 (**Table 1**). This result further indicates that sparsentan does not inhibit or enhance its own metabolism.[7]

Table 1. Pharmacokinetic Parameters for Midazolam and 1-OH Midazolam

Parameter	MDZ		MDZ-OH	
	Alone (N=28)	With Sparsentan (N=28)	Alone (N=28)	With Sparsentan (N=28)
AUC_{last}, ng×h/mL	18.8 (36.4)	18.5 (28.3)	5.69 (40.7)	4.47 (30.9)
AUC_{inf}, ng×h/mL	20.3 (36.6)	20.2 (27.9)	6.47 (38.3)	5.08 (25.7)[a]
C_{max}, ng/mL	7.07 (31.3)	7.44 (28.3)	2.53 (35.5)	2.20 (28.0)
t_{max}, h	1.0 (0.5-1.02)	0.5 (0.5-1.0)	1.0 (0.5-1.02)	0.5 (0.5-1.0)
$t_{½}$, h	4.23 (2.00)	4.15 (1.67)	2.24 (0.75)	1.84 (0.84)[b]
CL/F, L/h	98.3 (36.6)	99.2 (27.9)	n/a	n/a
V_z /F, L	531 (33.4)	543 (36.2)	n/a	n/a

[a]N=26; [b]N=27.
Data: Geometric mean (CV%) presented, except t_{max}, which is median (min-max) and $t_{1/2}$ which is arithmetic mean (SD).

Bupropion exposure (total and individual racimates) was reduced in the presence of sparsentan, suggesting sparsentan induces CYP2B6 (**Table 2**). Given these results, CYP2B6 substrates coadministered with sparsentan should be monitored and doses adjusted if needed.[7]

Table 2. Pharmacokinetic Parameters for Bupropion, R-bupropion, and S-bupropion

Parameter	BUP		R-BUP		S-BUP	
	Alone (N=28)	With Sparsentan (N=28)	Alone (N=28)	With Sparsentan (N=28)	Alone (N=28)	With Sparsentan (N=28)
AUC_{last}, ng×h/mL	786 (25.9)	516 (29.9)	702 (25.2)	468 (28.9)	77.9 (38.3)	44.0 (45.4)
$AUC_{0\text{-}inf}$, ng×h/mL	808 (25.5)	539 (29.3)	727 (24.7)	491 (28.2)	97.1 (37.1)[b]	54.1 (51.4)[b]
C_{max}, ng/mL	145 (31.5)	99.0 (31.9)	134 (31.3)	91.7 (31.6)	11.6 (43.4)	7.29 (44.3)
t_{max}, h	1.5 (1.0-2.0)	1.3 (0.5-2.0)	1.5 (1.0-2.0)	1.3 (0.5-2.0)	1.5 (0.5-3.0)	1.3 (0.5-3.0)
$t_{½}$, h	19.8 (4.8)	20.7 (8.1)	23.1 (5.9)	20.8 (8.0)	18.7 (7.4)[c]	14.0 (8.1)[a]
CL/F, L/h	186 (25.5)	278 (29.3)	103 (24.7)	153 (28.2)	772 (37.1)[b]	1390 (51.4)[b]
V_z /F, L	5110 (31.3)	7710 (36.8)	3300 (32.4)	4280 (35.3)	18500 (31.1)[b]	22300 (31.5)[b]

[a]N=26; [b]N=24; [c]N=25.
Data: Geometric mean (CV%) presented, except t_{max} is median (min-max) and $t_{1/2}$ is arithmetic mean (SD).

Sparsentan Population PK Analysis

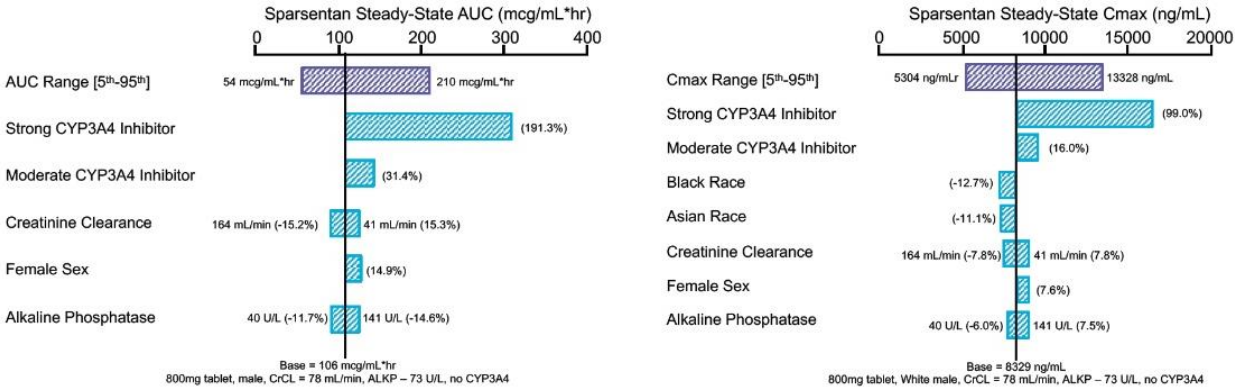
A population PK analysis of healthy volunteers (N=446) and patients with FSGS (N=195) described the PK of sparsentan and examined the impact of disease characteristics and concomitant medications on PK parameters. PK data were collected from 9 clinical studies, for a total of 10,957 samples from healthy volunteers and 1692 samples from patients with FSGS. Healthy volunteers received sparsentan doses ranging from 50-1600 mg/day; FSGS patients were dosed at 200 mg, 400 mg, or 800 mg/day.[8]

A two-compartment model with first-order absorption and absorption lag time found sparsentan $t_{1/2}$ to be 9.6 hours at steady state, apparent Vc/F of 69.5 L, and apparent CL/F of 5.27 L/h after a single 800 mg dose. CL/F increased to 7.21 L/h at steady state. Relative bioavailability of sparsentan was found to decrease with increasing dose.[8]

Effects of alkaline phosphatase and coadministration with moderate/strong CYP3A4 inhibitors were among the covariates examined. No effects were found with concomitant acid reducer, mild CYP3A4 inducer, CYP3A4 inducer, or P-glycoprotein inhibitor.[8]

In the final model analysis, univariate effects of each covariate on exposure at steady state in FSGS patients taking 800 mg/day sparsentan determined that coadministration of CYP3A4 inhibitors increased steady-state AUC. The increase in AUC was found to be 31% for moderate CYP3A4 inhibitors and 191% for strong inhibitors. Among all covariates examined, the effect of strong CYP3A4 inhibitors was the only one considered to be clinically meaningful (**Figure 2**).[8]

Figure 2. Tornado Plots Showing the Effects of Covariates on Steady-State AUC and C_{max}



Base, as represented by the black vertical line, refers to the predicted steady-state AUC of sparsentan in a typical FSGS male subject receiving an 800 mg tablet with ALP of 73 U/L, with CrCL of 78 mL/min, and not receiving a moderate or strong CYP3A4 inhibitor. Purple shaded bar shows the 5th to 95th percentile exposure range in the FSGS population. Blue shaded bars represent the influence of a single covariate (listed left) on the steady state exposure after once-daily sparsentan 800 mg. Blue bars are ranked in decreasing order of largest deviation from the base. Upper and lower values for each covariate capture 90% of the range in the population.

Impact of Sparsentan on Dapagliflozin

Interactions between multiple doses of sparsentan and single doses of the SGLT2 inhibitor dapagliflozin were assessed in an open-label, 1-sequence crossover study.[9]

- Plasma PK parameters were comparable before and after single-dose dapagliflozin alone and coadministration of sparsentan, suggesting that steady-state sparsentan concentrations following multiple-dose administration did not affect single-dose dapagliflozin PK[9]
- Compared to single-dose dapagliflozin alone, C_{max} and AUC values for dapagliflozin-3-O-glucuronide were 10-12% lower following coadministration of sparsentan, indicating a minimal effect of sparsentan on dapagliflozin metabolism[9]

Concomitant use of sparsentan and dapagliflozin was generally safe and well tolerated in healthy subjects, and no deaths or serious TEAEs occurred. Fewer TEAEs were reported with single-dose dapagliflozin or multiple-dose sparsentan alone compared to drug coadministration (ie, a single dose of dapaglifozin with multiple dose sparsentan).[9]

Abbreviations

ALP, alkaline phosphatase; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BUP, bupropion; CL/F, apparent clearance; C_{max}, maximum concentration; COX-2, cyclooxygenase-2; CrCL, creatinine clearance; CV, coefficient of variation; CYP, cytochrome P; DDI, drug-drug interaction; ERA, endothelin receptor antagonist; ET_A, endothelin-1 type A; FSGS, focal segmental glomerulosclerosis; HLM, human liver microsome; $IC_{50,}$ half-maximal inhibitory concentration; Ki, inhibitor constant; MDZ, midazolam; mRNA, messenger RNA; n/a, not applicable; NSAID, non-steroid anti-inflammatory agents; P-gp, P glycoprotein; PK, pharmacokinetics; RAASi, renin-angiotensin-aldosterone system inhibitors; SD, standard deviation; SGLT2, sodium-glucose transport protein 2; $t_{1/2}$, terminal half-life; TEAE, treatment-emergent adverse event; t_{max}, time to C_{max}; V_z/F, apparent volume of distribution.

References

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