FILSPARI® (sparsentan) Impact on Male Fertility

Summary

Prescribing Information

- FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity[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]
- General toxicity studies in rodents evaluated potential effects of sparsentan on spermatogenesis[5]

Study Data

Preclinical Studies

- In a fertility and embryonic development study in rats, oral administration of sparsentan at doses of 20, 80, and 320 mg/kg/day for at least 36 (females) and 49 (males) days did not result in any adverse effects on estrous cycles, mating, fertility, sperm evaluation or pregnancy incidences at doses up to 320 mg/kg/day, which provided approximately 10 and 14 times the AUC at the MRHD for males and females, respectively. Male reproductive organ toxicity was not evident in chronic toxicity studies at exposures up to 10 times and 1.3 times the AUC at the MRHD in rats and monkeys, respectively[1]
- In preclinical studies, sparsentan dosing in juvenile rodents beginning PND 7, PND 14-28, or PND 22 and continued through PND 90 showed that sparsentan had no direct effect on spermatogenesis[5]

Prescribing Information

FILSPARI REMS

FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity.[1]

Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.[1]

Fertility

In a fertility and early embryonic development study in rats, oral administration of sparsentan at doses of 20, 80, and 320 mg/kg/day for at least 36 (females) and 49 (males) days did not result in any adverse effects on estrous cycles, mating, fertility, sperm evaluation or pregnancy incidence at doses up to 320 mg/kg/day, which provided approximately 10 and 14 times the AUC at the MRHD for males and females, respectively. Male reproductive organ toxicity was not evident in chronic toxicity studies with sparsentan at exposures up to 10 times and 1.3 times the AUC of the MRHD in rats and monkeys, respectively.[1]

For more information, please refer to the attached Prescribing Information.

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.[6-8]

Preclinical Studies

Toxicity studies were conducted in juvenile rats, adult rats, and monkeys to assess the effect of sparsentan on multiple parameters of male fertility, including spermatogenesis, tissue necrosis, and vascular damage. Three studies in juvenile rats evaluated impact of initiating sparsentan on PND 7, PND 14 to 28, or PND 22 to 90 (adulthood). In additional studies, adult rats and monkeys were dosed for ≤6 months with sparsentan doses up to 320 mg/kg/day (rodents) and after 9 months of doses up to 200 mg/kg/day (monkeys).[5]

Study Data

Preclinical Studies

Overall, toxicity studies of male fertility did not find evidence of a direct effect of sparsentan on spermatogenesis. The PND 7 study found generalized vascular toxicity inducing minimum to severe degeneration and necrosis of vascular media, hemorrhage, and tissue necrosis in the testis and epididymis at sparsentan dose of 10 mg/kg/day. Effects were found on spermatogenesis and fertility parameters; however, these were considered secondary to the observed damage. In rats that were 1 week older, there were no effects on vasculature, sperm, or mating parameters at sparsentan doses up to 60 mg/kg/day.[5]

Other than findings from the PND 7 study, histopathologic assessment found no effects of sparsentan on spermatogenesis or damage to testis or other male reproductive tissues, indicating that sparsentan was not toxic to reproductive organs or the spermatogenic process.[5]

Abbreviations

AT_1, angiotensin II type 1; AUC, area under the curve; EED, early embryonic development; ET_A, endothelin-1 type A; GD, gestation day; MRHD, maximum recommended human dose; PND, post-natal day; REMS, risk evaluation and mitigation strategy.

References

1. FILSPARI. Prescribing information. Travere Therapeutics Inc; February 2023.
2. Komers R, Gipson DS, Nelson P, et al. Efficacy and safety of sparsentan compared with irbesartan in patients with primary focal segmental glomerulosclerosis: Randomized, controlled trial design (DUET). *Kidney Int Rep*. 2017;2(4):654-664. doi:10.1016/j.ekir.2017.02.019
3. Raczynska A, Pawlowicz-Szlarska E, Nowicki M. Sparsentan–a dual antagonist–literature review on endothelin and endothelin antagonists. *Nephrol Dial Pol*. 2021;25:77-82.
4. Trachtman H, Nelson P, Adler S, et al. DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754. doi:10.1681/ASN.2018010091
5. Sparsentan (RE-021) investigator's Brochure. 2021.
6. Nagasawa H, Suzuki H, Jenkinson C, et al. Sparsentan, the dual endothelin angiotensin receptor antagonist (DEARA), attenuates albuminuria and protects from the development of renal injury to a greater extent than losartan in the gddY mouse model of IgA nephropathy: A 16-week study. Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.
7. Nagasawa H, Suzuki H, Jenkinson C, et al. The dual endothelin type A receptor (ET_AR) and angiotensin II type 1 receptor (AT_1R) antagonist, sparsentan, protects against the development of albuminuria and glomerulosclerosis in the gddY mouse model of IgA nephropathy. Poster presented at: ERA-EDTA Virtual Congress; June 6-9, 2020; Virtual Meeting.
8. Bedard P, Jenkinson C, Komers R. Sparsentan protects the glomerular basement membrane and glycocalyx, and attenuates proteinuria in a rat model of focal segmental glomerulosclerosis (FSGS). Abstract presented at: ERA-EDTA Congress; May 19-22, 2022; Paris, France.